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## Original Communications\*

### THE USE OF AN ANTERIOR PITUITARY LUTEINIZING SUBSTANCE IN THE TREATMENT OF FUNCTIONAL UTERINE BLEEDING†

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ONE of the most frequent and most difficult problems in gynecology is the management of cases of functional uterine bleeding, more particularly in young patients, in whom the importance of preserving the menstrual and reproductive functions is obvious. With patients who are at or near the menopausal era, the problem is easier, for the reproductive lives of these patients have been lived, and there is no great disadvantage in bringing about the menopause by radium or x-ray therapy.

Functional hemorrhage is often, however, encountered at or near puberty, during the adolescent period, or at any age during the reproductive epoch. When sufficiently severe, curettage is usually indicated for both diagnostic and therapeutic reasons. By this means hemorrhage, of even alarming character, can ordinarily be checked, temporarily at least. Unfortunately, recurrence takes place in the majority of cases, often soon after operation; in other cases perhaps not for many months. The gynecologist is then usually called on to decide between repetition of the curettage and treatment by radium. Efforts at organotherapy may of course be made, but up to the present time these have usually been found unsuccessful.

\*NOTE: It was not found possible to include in this issue of the JOURNAL all of the papers read at this year's annual meeting of the American Gynecological Society. The remaining papers, together with the discussions, will be published in the November and subsequent issues.

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In spite of the great advances in radiotherapy during recent years, the consensus of opinion among conservative gynecologists and radiotherapists is that radium treatment should be a last resort in young persons. This in spite of the fact that a proper regulation of the dosage will usually prevent a permanent effect on the menstrual function, and that recent work appears to indicate that no deleterious effect is produced upon the product of conception, if pregnancy supervenes at a later date. It is a well-known fact, however, that the individual variation in the reaction to radium is very great. In some patients the ovarian function is hard to "kill," while other patients are so susceptible that even small doses of radium may bring about permanent cessation of function.

For this reason, many gynecologists have preferred to treat the great majority of such cases with curettage, repeated as often as the severity of the bleeding may indicate. By this plan most patients may be tided over until a readjustment of the disordered endocrine balance takes place. That a tendency to spontaneous readjustment is common is shown in the many milder cases which recover without any treatment whatsoever, or after a single curettage. In several previous papers<sup>1</sup> the clinical characteristics of this type of bleeding, together with the characteristic ovarian and endometrial findings, have been fully elaborated, so that they need not be here discussed.

Several facts, however, are worthy of reemphasis as bearing upon the plan of treatment we are proposing. The ovaries of these patients show an absence of corpora lutea and a persistence of the unruptured Graafian follicle. This would at once suggest that the ovarian disturbance consists of a persistence and relative excess of the follicle stimulus, with an entire absence of the progestin phase normally contributed by the corpus luteum.

This belief is confirmed by the findings in the endometrium of such cases, for there is never any evidence of the secretory activity which progestin produces in an endometrium previously primed with folliculin. That such a previous priming is necessary is indicated by the work of Allen,<sup>2</sup> Hisaw and Leonard,<sup>3</sup> and others. It is the constant, prolonged, growth stimulus of the follicle hormone, without the secretory topping-off normally brought about by progestin, which is responsible for the type of endometrium seen with functional hemorrhage. Almost always it assumes the form of hyperplasia of the endometrium, characterized perhaps most conspicuously by its "swiss-cheese" gland pattern, as has been emphasized in the previous papers above alluded to.

The term hyperplasia is perhaps not an altogether happy one for this endometrial picture, for in only a fraction of the cases is there an overgrowth of the endometrial elements. The condition really represents a persistence and an exaggeration of the picture seen in the so-called interval phase of the endometrium. It is this phase which

corresponds with the period of estrus in the lower animals, and, like the latter, it is associated with full maturation of the follicle in the ovary. If the follicle fails to rupture, a corpus luteum is of course not formed, so that the estrus type of endometrium does not, as normally, pass on into the pregravid or secretory type produced by the corpus luteum. The continued effect of the follicle hormone, on the other hand, produces the hyperestrous picture commonly designated as hyperplasia of the endometrium.

Characteristic as this endometrial picture is of these cases of functional bleeding, it is not such a simple matter to explain the mechanism of the bleeding. Schröder<sup>4</sup> believes that the hemorrhage occurs from very small localized areas of necrosis on the surface, but we have not been able to convince ourselves of the correctness of this view, although such areas of necrobiosis and thrombosis are often noted. It would be hard to believe that such punctate areas can produce the extremely abundant hemorrhages often seen. It seems more likely, since there is no such desquamation as with normal menstruation, that some change in the permeability of the blood vessels must be chiefly responsible for the bleeding. Just how this is brought about cannot be said.

That the endometrial lesion in itself cannot be responsible for the bleeding is indicated by the fact that exactly the same histologic picture may be found with amenorrhea. This observation, which we would formerly have looked upon as heretical and paradoxical, has been made by us now in a small number of instances. This number would no doubt be greatly increased if we had more frequent opportunity to study the endometrium in amenorrheic patients. The fact that hyperplasia is found in some cases of amenorrhea would seem to speak against Schröder's explanation of the source of bleeding in this condition. We believe that the cases of amenorrhea in which hyperplasia of the endometrium is found are the same group as those to which Zondek<sup>5</sup> gives the designation of "polyhormonal amenorrhea." In this group he finds an excess of the follicle hormone even though the patient is amenorrheic. Quantitative studies of the hormone content are therefore not by any means of decisive importance in differentiating the type of disorder or in indicating the treatment to be followed.

The reason for this confusion lies, of course, in the rather intricate and as yet poorly understood hormone interrelationships of the ovary and other endocrine glands, particularly the anterior pituitary. This is not the place to discuss these at length, although they are touched upon in a later paragraph. This ovario-hypophyseal interaction is no doubt chiefly responsible for the alternating phases of long continued amenorrhea and persistent bleeding seen in some patients, especially as the amenorrheic phase is often combined with an adiposity similar to that seen in the familiar adiposo-genital dystrophy.

One of our patients offers a striking exemplification of this group. She had been curetted a few years ago for profuse bleeding, the endometrium showing a typical hyperplasia. Following this she exhibited periods of amenorrhea lasting as long as seven months, with an occasional normal menstrual period. At the same time she gained a great deal of weight, the fat distribution being of the so-called hypopituitary type. Six months ago she again began to suffer with profuse menstrual bleeding, lasting from two to two and a half weeks, with cessation for only a few days before the advent of the succeeding period. At the same time there was a moderate loss of weight. Since hyperplasia may be associated with either amenorrhea or excessive bleeding, it seems quite certain that some other element, as yet not known, must be added to the follicle hormone excess apparently responsible for the hyperplasia. What this additional factor is we do not know, but it is obviously to be looked upon as a bleeding factor, as will be discussed later in this paper.

The participation of the pituitary in the etiology of functional hemorrhage is further suggested by the fact that a considerable number of cases appear to follow full-term pregnancy or miscarriage. It is a well-known fact that the anterior hypophyseal lobe undergoes marked hypertrophy during gestation, and to this, indeed, are attributed the acromegaloid changes at times seen in late pregnancy, such, for example, as enlargement and coarsening of the features. These acromegaloid changes commonly disappear shortly after delivery, but the occasional case passes on into a genuine acromegaly. Other favorite periods for the development of the latter disease are puberty and the climaacterie, when again there occur pronounced changes in pituitary activity.

These observations are of course only suggestive, as far as a possible corresponding rôle of the anterior pituitary in the etiology of functional bleeding is concerned. They are given no little support, however, by the recent work of Smith and Engle,<sup>6</sup> and Zondek and Asehheim,<sup>7</sup> demonstrating the subordinancy of the ovarian function to that of the anterior hypophysis. An observation of great importance, and one which we stress because of its bearing upon our immediate topic, is that recently made by Hartman, Firor, and Geiling<sup>8</sup> as to the immediate cause of the uterine bleeding in monkeys. It has been generally assumed that menstrual bleeding is due to the withdrawal of the corpus luteum hormone with the beginning of retrogression in that structure. The cause of this retrogression is still unexplained. The studies of Hartman, Firor and Geiling, however, lead them to conclude that the cause of the uterine bleeding is a positive and not a negative factor, i.e., that it is due to "an active substance originating outside the ovaries." Their experiments convince them that this substance is originated in the anterior hypophysis. They show that the "administration of anterior lobe hormone in any form—implants of fresh gland,

or intraperitoneal injection of triturated gland tissue by trocar, or injections of acid or alkaline extract—all result in bleeding, whether the animal be normal, sick and amenorrheic, castrated or hypophysectomized, old or young.” The recent report of Hofbauer,<sup>9</sup> again, indicates that injections of an anterior pituitary extract can bring about in animals (guinea pigs) an endometrial picture resembling hyperplasia.

The observations of Hartman and his associates may be accepted as demonstrating that uterine bleeding in the monkey may occur under the influence of a factor outside the ovary, and probably originating in the anterior pituitary lobe. We do not believe, however, that it can be accepted that this same factor is responsible for the bleeding of normal menstruation. The bleeding which the above named observers produced seems rather comparable to that occasionally observed in women in the interval period; i.e., the period corresponding to estrus in the lower animals. Following this period in the human cycle, however, there comes a prolonged up-building phase produced by progestin, which apparently possesses anti-ovulation and anti-bleeding properties. What causes the cessation of the progestin phase and the supervention of bleeding is not known. While a positive bleeding factor may here again be concerned, this has not yet been demonstrated, and it is still possible that the bleeding may be a withdrawal phenomenon, dependent upon the rather abrupt removal of the progestin influence.

The observation in the work of Hartman and his associates which we would especially emphasize is that “the threshold for the bleeding phenomenon is immensely lower than that for growth and congestion of the uterus and ovaries.” They were able to produce bleeding in normal or ovariectomized animals with very moderate dosage of the anterior lobe hormone, and the same result is obtainable, as many others have found, with moderate doses of the follicle hormone. With the latter there is of course no effect upon the ovaries, if these be present.

This is in line with the important studies of Marrian and Parkes,<sup>10</sup> who found that, in 50 per cent of the ovariectomized mice which they studied, the amount of follicle hormone necessary to produce copulation and the uterine changes of estrus is about two hundred times that required to induce the vaginal cornification changes which constitute the standard for the Allen-Doisy test. They very properly emphasize that the application of this fact to the human problem would indicate that in the woman, weighing about 2000 times as much as the mouse, the amount of follicle hormone required to produce histologic changes in the uterus would be  $2000 \times 200$ , or 400,000 mouse units. This observation, as they remark, makes our present efforts at follicle hormone therapy seem very fantastic.

Practically all investigators who have studied the question agree that the anterior lobe produces two hormones, one of which is concerned with

follicle growth and ripening, the other with the process of luteinization. Evans and Simpson,<sup>11</sup> Crew and Wiesner,<sup>12</sup> and Zondek<sup>13</sup> all agree on this point, although they apply different designations to the two substances. In addition to these two, there are of course still other hormones produced in the anterior lobe, but with these we are not directly concerned in this paper. To adopt Zondek's classification, his prolan A has to do with the motivation of follicle ripening and maturation, while his prolan B fulfills the same rôle with regard to luteinization.

It is now well known that the function of the anterior pituitary increases, in what Zondek speaks of as an explosive fashion, with the occurrence of pregnancy. Large amounts of the anterior pituitary hormones are produced, so that large amounts are found in the urine. It is on this overflow of the hormones in the urine that the Aschheim-Zondek test is based. Zondek<sup>14</sup> was able to separate the pituitary hormones in aqueous solution from the urine of pregnant women, giving this watery extract the name of "prolan." Of the five anterior pituitary hormones which have been described, at least three are contained in Zondek's prolan. These are the follicle-stimulating hormone, or prolan A, the luteinizing hormone, or prolan B, and the metabolic hormone. The growth hormone alone is absent. The two important hormonal principles, prolan A and prolan B, cannot as yet be readily separated, although the former has been obtained in unmixed form, and Aschheim is said to have obtained the B principle from the gland itself. The dominant action of the urine in pregnancy, especially in the earlier stages, is that characteristic of prolan B., i.e., luteinization. The injection into a rabbit of prolan, containing both principles, brings about extensive luteinization, so that according to Zondek,<sup>15</sup> the ovary can be almost converted into a mass of lutein tissue. The ovaries, normally the size of lentils, become as big as cherries. At the same time there is a profound effect upon the genital organs, the uterus becoming much enlarged and of bluish-red hue, like that seen in early pregnancy. The endometrium presents a picture like that seen in early pregnancy.

It is these changes in the ovary and uterus which we wish to stress, for upon them was originally based the treatment we have been employing in functional bleeding. As has been said, the characteristic ovarian finding in these cases is the entire absence of any lutein tissue, so that, as might be expected, one never finds in the endometrium any of the changes known to be due to the effect of progestin, and only progestin, as shown by Corner and Allen.<sup>16</sup> This is especially true as regards the complete absence of any secretory activity in the epithelium. One of us (Novak)<sup>17</sup> has repeatedly urged that if an active extract of the corpus luteum were available, it should be possible to transform the nonsecretory hyperplastic endometrium of these bleeding cases into a secretory, pregravid type, with probable completion of the cycle and

cessation of the bleeding. So far, however, progestin has not been prepared in a form suitable for administration to the human being. Even if it were, its effect, like that of the follicle hormone, would be a purely substitutional one, for it apparently has no effect upon the ovary.

With the demonstration of the two separate hormones in the anterior pituitary lobe, it seemed to us that if it were possible to secure a preparation of the luteinizing principle, an even more fundamental plan of treatment would be opened up to us. With such a preparation it should be possible to convert the granulosa cells of the ovary into lutein cells, so that the latter would themselves produce the progestin lacking in the cases with which we were attempting to deal.

Such a preparation has been made available to us through the courtesy of the Department of Experimental Medicine of Parke, Davis & Company, although we believe that it was intended primarily for use in cases of amenorrhea. It seemed to us, however, that a far more important field for its use was in the treatment of functional hemorrhage. Amenorrhea is rarely a serious condition, and, although the new preparation would be a rational one to employ as a part of the treatment of amenorrhea, the indication seemed less specific and less important than in the bleeding cases.

In regard to the method of preparation of the luteinizing hormone used in this work, it may be stated that the urine from pregnant women is concentrated and subjected to precipitation with water-soluble organic solvents, such as alcohol and acetone, thereby removing a large amount of inert material. In later work dialysis methods have been applied. The method is still admittedly imperfect, but will no doubt be improved from time to time. It can already be stated that the methods initially described by Zondek are unsuitable for the practical preparation of a stable product, but progress is being made in developing new methods.

The preparations which we have used have been very variable in their potency in animals, some producing marked luteinization while with others the response has been much feebler. Our clinical results have almost paralleled these laboratory variations. The chief difficulty in the preparation of the substance has been in its rather rapid deterioration, although it is hoped that this will soon be overcome. It is probable, too, that very potent luteinizing preparations will soon be available in water-soluble form. Loeser<sup>18</sup> has been able to secure very effective preparations of prolan in powder form ("Aceton-trockenpulver"), although this is not water-soluble.

The material we have been using has been entirely freed of the follicle hormone. It is certainly nontoxic and nonirritating. In short, it is apparently a perfectly safe preparation of the urine of pregnancy, and this urine is known to contain the anterior pituitary hormone the effect of which is desired. Though both prolan A and prolan B are present, the dominant action is that of the luteinizing hormone. This is

exactly what we would expect when we consider that in early pregnancy the ovary contains a large amount of lutein tissue, represented by the corpus luteum of pregnancy and perhaps also by a considerable amount of theca lutein tissue. Furthermore, follicle activity is in abeyance at this stage. The explanation for this dominantly luteinizing effect of prolan is given by the work of Wiesner,<sup>19</sup> who found that prolan A rapidly deteriorates, soon losing its effect on mere standing. Furthermore, Wiesner states that the maximum effect of prolan A is reached long before that of prolan B, so that the effect of their combined administration in maximum dosage is that of the prolan B; i.e., luteinization. The preparation we have been using is therefore standardized for prolan B, the standard of potency being the production of definite luteinization changes in the ovary. The unit of dosage is the rat unit, this being the smallest amount bringing about such changes in a rat of standard weight.

When it comes to the question of dosage for clinical administration, we have had no standards for guidance. On the basis of Wiesner's work, large doses seemed desirable, and we have rather arbitrarily chosen 200 rat units as a daily dose for the intramuscular treatment in our cases. This is somewhat larger than that used by Zondek<sup>20</sup> in the treatment of a different group of cases, but we felt that this was justified because of the luteinizing effects of maximum doses (Wiesner), by the greater urgency of bleeding as a symptom, by the harmlessness of the preparation, and by the presumable freedom from certain risks emphasized by Zondek in the management of amenorrhea. In the latter condition, according to Zondek, there is danger, if too much is used, of producing luteinization before ovulation can occur, and thereby imprisoning the ovum within the luteinized follicle. This occurrence would, we believe, be of no significance in cases of functional bleeding, when the end desired is luteinization on as rapid and extensive a scale as possible, and without regard to whether or not ovulation takes place.

Our original idea in the use of this preparation, therefore, was to try to bring about luteinization of the granulosa cells in the ovary, with the mobilization of progestin, and thus to transform the characteristic "stationary hyperplasia" picture in the endometrium to a pregravid one. The explanation of the good results which we have obtained, however, is almost certainly not so simple as this. For example, in some of our cases in which bleeding had been present for many weeks, cessation was noted after even a single injection. The smallness of the dose, and, even more, the rapidity of the effect, would seem to preclude the mechanism we had presupposed. The most likely explanation would seem to be that the effect is exerted upon the still unknown bleeding factor which, as already stated, determines the occurrence or non-occurrence of bleeding with hyperplasia of the endometrium. Whatever the factor is, it would seem that it is in some way bound up with

a disturbance in the balance between the two anterior pituitary hormones. An excess of the bleeding factor and a deficiency or absence of the lutein tissue and its hormone appear to go together.

The administration of prolan B fills a physiologic gap, and appears to exert upon the bleeding a far more rapid and precise effect than it can possibly exert on the ovarian and endometrial histology. This is in line with the conclusions of Hartman and his coworkers<sup>8</sup> and of Marrian and Parkes,<sup>10</sup> indicating that the threshold of uterine bleeding is at least 200 times less than that of the production of actual histologic changes in the genital mucosa. In a converse fashion, it would seem that the bleeding in cases of the functional type which we are discussing is much more quickly influenced than is the endometrial or ovarian histology. These considerations show the impossibility as yet of a complete explanation of the good results obtained in our cases, because it is still impossible to explain the mechanism of the bleeding in cases of this group. We do believe, however, that the method of treatment is a rational one, being in conformity with what we thus far know of the puzzling interrelationships of the anterior pituitary and gonadal hormones. Loeser and others have been able to prepare very potent extracts of prolan in dry powdered form (acetontrockenpulver), and this may be the solution of our difficulty. We have been given assurance by the Research Department of Parke, Davis and Company that water soluble solid extracts of undoubted luteinizing potency can be prepared, and we hope to be able to improve our results when these are made available.

#### RESULTS

In all we have thus far treated 51 cases by this method. These patients were observed in the private practice of one of us, in the out-patient gynecological clinic of the Johns Hopkins Hospital, and in the practices of a number of colleagues. Of the 51 patients no less than 32 had had previous curettements, with no benefit, or at best, only temporary relief. In a considerable number more than one curetting had been done; in several, as many as four. The ages of the patients varied from fifteen to fifty-one years, but only 10 of these cases were of the menopausal type. In other words, the majority of the patients were of an age at which radiotherapy would have been undesirable.

In all but 7 patients of the series the bleeding was checked, in many with astonishing rapidity. Moreover, we feel justified in stressing the fact that we have worked with preparations of varying potency, as determined by laboratory studies of their luteinizing properties. Our first batch of material, for example, was reported as being strongly luteinizing, and 27 of the 29 patients for whom it was used were promptly relieved of bleeding, even though this, in some patients had been present for many weeks. The other 5 failures were all noted in cases in which we had been told to expect lower potency.

In some of our patients the bleeding was in the nature of hypermenorrhea; i.e., the menstrual periods were much prolonged and excessive. In other cases the patients have had metrorrhagia of greater or less duration. If bleeding was in progress when the patient came under observation, the injections were begun at once. If the hypermenorrheic patient was not bleeding at the time, the first injection was given as soon as the flow reappeared.

In 14 patients the bleeding was checked after one injection; in 14 after two; in 9 after three; in 3 after four; in 3 after five; and in 1 after six. These results, as we shall emphasize later, have to do with the immediate bleeding attack alone, and are not meant to apply to the matter of permanent relief. In a considerable proportion of these cases, the patients were treated during more than one bleeding period, but these "repeats" are not included in the above figures.

#### IS THE TREATMENT OF TEMPORARY OR PERMANENT VALUE?

This question we cannot as yet answer, as we have been employing the plan only a few months. Even if the beneficial results of the treatment pertain only to the bleeding attack, it would still be of great value. There are few women who would not prefer a number of hypodermic injections to curettage or radiotherapy. However, there is reason to believe that the benefits of the treatment may be of more lasting value. In a few cases in which, after obtaining good results in one bleeding attack, we have persuaded the patients to go through the next menstrual period without treatment, the flow has not been abnormally free. Furthermore, if we are successful in obtaining more strongly luteinizing preparations, we believe that we may be able to produce actual luteinization in the human ovary just as this can be produced in that of the laboratory animal. We are hoping that opportunities may later come of studying the ovaries and the endometriums of patients who have been subjected to this method of treatment, as this would give us direct evidence as to whether one can produce actual luteinization in the ovary, and, in the uterus, the conversion of the hyperplastic endometrium into a pregravid one.

#### THE INTRAVENOUS USE OF PROLAN

When we began our work, we were not aware that any previous attempts had been made to treat functional hemorrhage by preparations of prolan. In a recent publication, however, Zondek<sup>21</sup> mentions that he has employed prolan intravenously for this purpose, and with good results. His object, like ours, was to bring about luteinization in the ovaries, and also, as he says, the prevention of follicle ripening. He gives no details of his results. We do not see the necessity for the intravenous method of treatment, especially if, as we believe, the good results are brought about by an effect upon a factor much more readily influenced than the histologic condition of the ovaries.

It is possible that the intravenous method may be far more potent in the production of ovulation than the subcutaneous route, as in the case of the rabbit, but this has not been established for the human being. If good results can be obtained from the simple intramuscular injections which we have been employing, this route would seem the preferable one. However, we hope later to be able to compare the results obtained by the two methods of administering the substance.

The only other report on the subject which we have been able to find is a short one by Martin<sup>22</sup> on the treatment of 12 cases of various types of hemorrhage by prolan. Its use in this group, which included several of functional hemorrhage, was apparently semi-empiric, although good results were obtained in 10 of the cases.

#### SUMMARY

The present report deals with the treatment of 51 cases of functional uterine hemorrhage by an anterior pituitary luteinizing principle derived from the urine of pregnant women. In 44 of these the treatment was successful in checking the bleeding, even though some of our patients were treated with preparations of somewhat uncertain luteinizing potency. Most of the failures were in this group. Previous efforts at the organotherapy of this condition have been unsuccessful. Radiotherapy is very undesirable in young women, so that, because of the frequent intractability of functional hemorrhage, many patients have had to submit to repeated curettage.

The characteristic ovarian finding in these cases is an absence of corpora lutea. The administration of progestin, if this were available, would be a rational plan of treatment. Progestin is not yet available for human administration, and its effects would, moreover, be purely substitutional, as it has no effect on the ovaries. The administration of the luteinizing hormone of the anterior pituitary (prolan B) can be expected to be more fundamental in its effects. This substance has been shown by laboratory studies to produce striking luteinization in the ovary, and the secretion of the lutein cells is progestin, the element lacking in functional hemorrhage. The hormone can be obtained from the urine of pregnant women, although its extraction is as yet somewhat difficult, and the preparations with which we have worked have been of very variable potency.

With strongly luteinizing preparations, it has been possible to check functional hemorrhage in 27 of 29 cases. In 14 of our 51 cases the bleeding has ceased after a single injection, and in 12 after two injections. A large proportion of these cases were of the intractable and recurrent type, many having had from one to four or more curettings. With less potent luteinizing preparations, the results have been less impressive, but on the whole satisfactory. Our experience with the entire group has convinced us of the value of the treatment in functional hemorrhages, and of its even greater future possibilities. This opinion seems a compelling one even though, in the nature of things, the results cannot be controlled with the precision of laboratory experiments.

The rapidity of the effect in many cases makes it seem certain that the immediate effect, at least, is not brought about through the production of lutein tissue and progestin by the ovary. We believe that this immediate effect is exerted upon the still unknown bleeding factor

which is the immediate cause of the bleeding in functional hemorrhage, and which is influenced by far smaller dosage than would be required to produce histologic changes in the ovary. This view we base upon recent investigations on this bleeding factor and on studies upon the relative dosage required to bring about the various stages of estrus. These are discussed in the paper.

It is hoped that improvements in results will come with improvements in the methods of preparation of this substance, and, quite possibly, in its preparation in water-soluble solid form. Whether the intravenous method of administering prolan will yield results more favorable than the intramuscular route remains to be seen.

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Haberlandt was the first to suggest the possibility of producing temporary sterilization by means of the injection of hormones. It was found that the substance which inhibits the ovary may be found not only in the ovary but also in the placenta. A few years ago the author outlined the clinical and eugenic indications for temporary sterilization. Since then, hormonal sterilization has been performed in women in Russia by means of injections of placenta extract. The difficulty consists in making a potent yet harmless preparation for clinical purposes. The substances used by Haberlandt in animal experiments are too weak for clinical use, but he hopes that the inhibitory element of the female sex hormone will soon be separated from the stimulating element and will be available for the purpose of temporary sterilization.

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## THE RESULTS OF THE RABBIT OVULATION TEST IN THE DIAGNOSIS OF PREGNANCY\*

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### THEORY AND METHOD OF THE TEST

**I**N DESCRIBING our results with the rabbit ovulation test for pregnancy it will not be necessary to discuss the biologic basis upon which it rests, since the reader will find the subject well covered in a recent review by Aschheim (1930) dealing with the Aschheim-Zondek test, and in another by Friedman upon the rabbit test, of which he is the original proponent. It will suffice to say that the urine of pregnant human females, after about the third week, contains large quantities of substances resembling in their effects the gonad-stimulating hormones of the anterior lobe of the hypophysis. The Aschheim-Zondek test and the rabbit ovulation test are simply two different methods for obtaining evidence as to the presence or absence of the hormones in question, in a given sample of urine. The former is performed by giving daily injections of the urine in question to immature mice; at autopsy after five days the ovaries are examined directly for signs of stimulated growth and function. The rabbit test of Friedman depends upon the fact that rabbits, which (unlike most other mammals) do not normally mature and rupture their Graafian follicles except after copulation, may be made to ovulate without copulation by giving them an intravenous injection of the gonad-stimulating hormones as found in the hypophysis and in the pregnant urine.

Having ourselves a long experience in the study of the physiology of reproduction, we were at once interested in Friedman's suggestion in his paper of 1929 that the facts outlined above might be used for a rapid and accurate clinical test for pregnancy. One of our students, Mr. J. J. Jares, was, we believe, the first to confirm and extend Friedman's results, and in the spring of 1930 we began intensive trial of the method in the clinic. Owing to the fact that the work reported in this paper was begun and largely completed before the publication of other reports upon the test, we were under the necessity of working out for ourselves the practical details and standards of the test. For this reason our routine differs much from that given by Schneider and to a less degree from that of Friedman and Lapham.

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*Technic of Test.*—Ordinary voided specimens of urine are received from the clinic and stored in the laboratory ice box until used. Positive specimens remain active for many months, so that they may be sent by mail from distant points, or reserved for retesting, without risk. The test is begun by giving to a suitable rabbit, usually (for convenience) at about 5 P.M., an intravenous injection, without sterile precautions, of 5 c.c. of the urine.

We use only fully adult female rabbits, of four pounds weight or over, which have been kept in strict isolation for one month or more. The principles upon which this practice is based are clearly given by Friedman and Lapham on page 406 of their paper. Trained investigators familiar with the reproductive physiology of rabbits, and technicians of long experience with the test may, as stated by Friedman and Lapham, relax the rule in emergencies, but this would be unsafe for others using the test.

The next morning at 9:00 A.M. or later, that is to say at sixteen hours or more after injection, the rabbit is prepared for operation under ether anesthesia by aseptic technic and explored through a mid-line abdominal incision. A positive result is determined by the presence in the ovaries of recently ruptured Graafian follicles, indicated as shown in the Plate I, Fig. b, by bright red elevations of conical form, a millimeter or two in diameter, having usually a very small depression in the center. Inexperienced observers may possibly find it difficult to distinguish these ruptured follicles from large unruptured follicles which are sometimes present, especially if the vessels in the latter are somewhat engorged. The unruptured follicles are rounded rather than conical or mammillary in form, show no central stigma or depression, and are much paler and clearer. A hand lens may aid in the discrimination. Still more confusing are the rather frequently present hemorrhagic unruptured follicles, more or less peculiar to the rabbit. These are usually of dull red color approaching black, and are generally smaller and less prominent than the ruptured follicles. As a safeguard for beginners we have illustrated such hemorrhagic follicles in Plate I, Fig. a.

Another finding sometimes encountered is that of very large clear follicles, apparently just on the verge of rupture, suggestive of some ovarian stimulation. In the presence of such findings we have in a number of instances repeated the test, using a larger quantity of urine (10 c.c.) and allowing a longer period to elapse before the animal was explored. This has not changed the results, and we have reported such findings as negative.

After observation of the ovaries the abdominal wound is closed with silk and the animal returned to isolation for subsequent use. Mr. Jares found that a second ovulation may be induced within a few days of the first, and therefore, if necessary, the animals can be used again without a long interval, but in order to spare them the ill effects of too frequent exploration it is our custom to use each animal about once a month. They withstand, on the average, five or six explorations before adhesions or bad healing terminate their usefulness. We have had only one instance of difficulty due to toxicity of the urine.

It will be noted that the chief difference between our routine and that of Friedman and Lapham is that we read the test after sixteen hours while they feel that it is advisable to wait forty-eight hours to eliminate the possibility of delayed reactions. The high level of accuracy, attained in our investigation, quite equaling that of the Aschheim-Zondek test and of the rabbit ovulation test as applied by Friedman and Lapham, seems to indicate that the shorter test period does not lead to inaccuracy. One of the great advantages of the rabbit test over the Aschheim-Zondek test is the possibility of making

the diagnosis overnight, and in case of doubt a test may be checked by a repetition within forty or forty-two hours from receipt of the original specimens.

Schneider uses young rabbits (sixteen weeks old). At this age the animals are not quite mature sexually, and thus a positive test involves not only ovulation but also preliminary changes in the ovary to bring it into the mature state. Presumably for this reason Schneider waits thirty hours before autopsying his rabbits.

Experience alone will tell whether it is more economical to examine the rabbits, as we do, by operation rather than by autopsy. It cuts down turnover in the colony and lowers the purchase cost per test, but requires a trained technician and sterile supplies for the operations.

While we have recently made use of this procedure as a diagnostic aid in a considerable number of cases, the object of the present study has rather been to determine its real value from the standpoint of clinical diagnosis, and to learn what possible sources of error, if any, may be present. We have therefore carried out observations on a relatively large series of women in various stages of pregnancy, and the puerperium, on abnormal pregnancies, on women presenting menstrual disturbances, as well as on a series of patients presenting a miscellaneous variety of pathologic lesions.

A small series of observations, 16 in all, were made on women at the end of pregnancy, daily specimens of urine being obtained from the same women for the first few days of the puerperium. This was done to determine how long the reaction remained positive after pregnancy had terminated. In this series, all gave a positive reaction during pregnancy, the reaction becoming negative within twenty-four to seventy-two hours postpartum, though in only two instances did it remain positive for a longer period than forty-eight hours. This time factor differs somewhat from that observed in the Aschheim-Zondek reaction, which only becomes negative seven to eight days after delivery.

Those women upon whom observations were made in the early periods of their pregnancies represent a most important group from the diagnostic standpoint. Tests were carried out upon the urine from eighteen women who were presumably in the first month of pregnancy. True, the exact duration of the pregnancies was not known, and had been estimated from the menstrual history and the lack of development of the uterus; but inasmuch as in all these women not more than thirteen days had elapsed since a menstrual period had been missed, and the uterus showed little or no change, it seems fair to assume that they were not more than four weeks pregnant. In three of the women only eight days had elapsed since the menstrual period had failed to appear. In all of these 18 cases a positive result was obtained. In 30 other women who from similar criteria were presumably from four to

eight weeks pregnant, the urine also gave a positive result. All of these women were observed subsequently and the diagnosis of pregnancy fully confirmed.

In addition to these, three other women were observed in whom ten to thirteen days had elapsed since the missed period, and who were also presumably in the first month of their pregnancies. Their urine gave a negative reaction at the first examination, but four to seven days later, the reaction became positive. Subsequent examinations confirmed the diagnosis of pregnancy. In these three instances, possibly conception had occurred at a slightly later date than in the first group. These findings would also indicate the advisability of repeating the test in the doubtful early case.

In three other women, who had myomatous uteri, and who were presumably from two and a half to three months pregnant, the test was also positive, and again subsequent examinations established the diagnosis of pregnancy.

Our earliest known case is worthy of special mention. This woman gave the history of having menstruated last on July 4, 1930. She was admitted to the hospital on account of a rather large myomatous uterus. Examination offered no suggestion of pregnancy and the urine was not tested. Hysterectomy was done on July 24, 1930, and on opening the uterus an early ovum, of not more than three weeks development, was discovered. (This is being prepared for embryologic study.) A specimen of urine obtained eight hours after operation gave a positive reaction.

The results obtained during pregnancy may be tabulated as follows:

FULL-TERM PREGNANCY AND PUERPERIUM		
16 observations		
During pregnancy	all positive	
Becoming negative	in 24 to 72 hours	postpartum
EARLY PREGNANCY		
During first month	18	all positive
4- 8 weeks	30	all positive
8-12 weeks	7	all positive
12-20 weeks	6	all positive
EXCEPTIONS		
3 cases 10 to 13 days past period	all negative	
4 to 7 days later becoming	all positive	
PREGNANCY WITH MYOMA		
2½ to 3 months	3 cases	all positive

Another important group of patients studied includes those women who presented certain abnormalities of pregnancy, and from the standpoint of assessing the diagnostic value of this procedure these have proved to be of particular value. Thirty-one observations were made on various types of abortions. In four women, two to three months pregnant, presenting themselves with the symptoms of threatened abortion, the test was positive. In 19 incomplete abortions 10 posi-

tive and 9 negative reactions were obtained. In all those who gave positive reactions, when the uterine cavity was explored, placental tissue was found still attached to the uterine wall, which on microscopic examination was found to be active living tissue, while in those who presented negative reactions, only decidua, or dead inactive placental tissue was obtained when the uterine cavity was explored. In six complete abortions, in which a curettage was performed several days after the abortion had occurred, a negative reaction was obtained in all cases. Microscopic examination of the curettings revealed no fetal tissue.

Two cases of missed abortion are of particular interest and the findings in these two patients may be briefly summarized as follows:

CASE 1.—Was first seen on July 11, 1930, when she was apparently four months pregnant. The ovulation test was positive. She was not seen again until September 30, 1930. At this time, it was found that the uterus had not increased in size, and a clinical diagnosis of missed abortion was made. The ovulation test at this time was found negative. On October 2, 1930, a vaginal hysterotomy was done, and the uterine contents removed. A mummified fetus, together with a completely infarcted placenta was removed. Microscopically it showed no active fetal cells.

CASE 2.—Patient was first seen on December 23, 1930, when she was apparently about three and one-half months pregnant, the ovulation test was positive. On January 9, 1931, she noticed slight bleeding, and ovulation test was negative. She was not seen again until February 27, 1931. At this time there was no bleeding, the uterus had not increased in size, and the ovulation test was again negative. On March 2, 1931, the uterus was emptied, and again a dead ovum with infarcted, inactive placental tissue was obtained.

In contradistinction to these findings, the results obtained in two women, near term, with dead fetuses in utero are of interest. In one instance, the child had died in utero and had been retained for at least a month, and in the other case for a somewhat longer period. The urine from each gave a positive reaction. Both were delivered spontaneously of well developed, but very badly macerated fetuses which had obviously been dead and retained in utero for a long period of time. In each instance, however, the placenta was not macerated, which is the usual finding in such circumstances, and microscopic examination revealed active living fetal tissue.

The results obtained in 6 cases of ectopic pregnancy are also of particular interest. Three gave positive reactions while the other three were negative. All 6 women were operated upon and the diagnosis definitely established. The three whose urine gave positive reactions were of the acute type and at operation active living fetal tissue was found partially attached to the ruptured tube. In the three who gave negative reactions, the symptoms were of much longer duration, and at operation no active fetal tissue was discovered.

One case of hydatid mole was observed. The summary of the observations made on this patient are as follows: A rather large hydatid mole was removed from the

uterus on May 12, 1930. We had just started working on this problem at the time and a specimen of urine was not obtained prior to operation. An ovulation test thirty-six hours after operation showed very large unruptured follicles in the rabbit's ovaries, evidently the result of some ovarian stimulation, but we considered it negative. On June 7, 1930 she returned to the hospital on account of rather free vaginal bleeding at which time a diagnostic curettage was done. The ovulation test was positive, and the microscopic examination showed one or two small hydatid vesicles, with active fetal cells present which were considered not malignant. Forty-eight hours later the test was still positive, but two subsequent examinations gave negative results. On July 17, 1930 she again returned to the hospital on account of some vaginal bleeding. She was again curetted for diagnosis. The ovulation test at this time was negative, and the curettings showed a normal endometrium with no fetal cells to be seen. The subsequent menstrual periods have been quite normal.

The results that we have obtained on these abnormal pregnancies correspond closely to those obtained in similar cases with the Aschheim-Zondek reaction, and by way of interpretation we may quote Aschheim, that "the reaction remains positive as long as living placental tissue is in biologic contact with the maternal blood."

Forty-eight observations were made on women who presented various disturbances of menstruation. Generally speaking, these were carried out as controls though in a number of them it was important to establish or exclude the diagnosis of pregnancy. Twenty-seven of them were women who presented themselves on account of amenorrhea. All were healthy women, the majority of whom had skipped one menstrual period by eight to fourteen days and in whom the possibility of pregnancy existed, while a few were approaching the menopause. All gave negative reactions and all menstruated normally subsequently. In eight other healthy women, who were seen on account of irregular menstruation, the reaction was also negative. It was also negative in thirteen other women, who presented themselves on account of inflammatory lesions in the pelvis associated with irregular bleeding. The symptoms in this latter group were slightly suggestive of ectopic pregnancy. In each instance pregnancy was satisfactorily excluded by subsequent observation or operation.

Eight observations were made on women who were seen on account of persistent, excessive vaginal bleeding. After curettage the uterine mucosa presented the typical picture of endometrial hyperplasia. Seven of them gave negative results, although in two of these unusually large follicles, apparently on the verge of rupture, were seen in the rabbit's ovaries, suggestive of some ovarian stimulation. Repetition of the test, using a larger amount of urine and allowing a longer time to elapse before exploration, gave the same result. In one instance, however, the reaction was definitely positive. This is the only positive reaction that we have obtained in a nonpregnant individual. The patient was a young girl, fifteen years of age, who was admitted on account of rather severe bleeding of puberty. Even this one positive

reaction may possibly be of some significance when we consider the possible relationship between overactivity of the anterior pituitary body and this type of functional bleeding.

In addition to the above, a small series of observations were made on a miscellaneous group of conditions which are tabulated below. All reactions were negative.

#### REACTIONS IN MISCELLANEOUS CONDITIONS

Normal women not pregnant	5 observations	all negative
Persistent vomiting not pregnant	2 observations	all negative
Advanced carcinoma	5 observations	all negative
(3 carcinoma of ovary, 2 carcinoma of cervix)		
Myoma uteri, not pregnant	3 observations	all negative
Aeromegaly, male	1 observation	negative
Hypopituitary, male	1 observation	negative
Froehlich's syndrome (boy)	1 observation	negative
Testicular tumor	1 observation	negative
Dermoid cyst	1 observation	negative
Acute appendicitis	2 observations	all negative
Discarded for lack of subsequent information	5 negative, 6 positive	

#### SUMMARY AND CONCLUSIONS

The results obtained from the urines of 196 women upon whom the rabbit ovulation test as suggested by Friedman was made are herewith presented. The findings correspond very closely to those reported in the use of the Aschheim-Zondek reaction, with apparently a very small percentage of error. Its advantages over the latter are found chiefly in the much shorter time necessary, its simplicity, and a possible economy of laboratory animals.

From our experience we believe that it should prove to be an extremely valuable and practical method for the early diagnosis of pregnancy. In our series, with the exception of a single case of endometrial hyperplasia, a positive reaction has always indicated the presence of active fetal tissue in biologic contact with the maternal blood stream, or very recently (not over seventy-two hours) separated from it.

A negative reaction does not entirely exclude the possibility of a pregnancy being present, since the intra- or extrauterine ovum may have perished, and been retained for some period of time.

It may prove to be of some value in determining the life or death of the ovum in the early months, though not its immediate death, and not in the later months of pregnancy.

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## THE CLINICAL IMPORTANCE OF THE SEX HORMONES\*

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THE vast amount of knowledge already accumulated on this subject, together with the existence of a number of excellent and full reviews, makes the task of a speaker a very difficult one if he attempts to produce something original for his audience. Again, as the American school of biologists and biochemists was almost entirely responsible for the reawakening of interest in this line of work, one cannot help feeling great diffidence about speaking on such a subject here. The work of Allen and Doisy, Corner and Evans is well known to all and has been reviewed innumerable times, while the work of Zondek and his group in Germany has also received considerable attention. It would appear that little remains to be said upon the subject from a general point of view, and I am, therefore, driven to talk to you about my own work and that which is being carried on in my department by my colleagues. It is felt that the existence of the already mentioned reviews and critiques will absolve the speaker from going over the older and more familiar ground.

### THE ESTRUS-PRODUCING HORMONE (ESTRIN OR THELIN)

We have labored almost continuously on this substance since the early publications of Allen and Doisy enabled workers to put their investigations on a quantitative footing with regard to standardization. It is with the latter that I should particularly like to deal. It will be remembered that the unit was defined as that amount of material which when injected subcutaneously into castrated animals was capable of producing estrus. Some workers employed rats, others mice, and the general method adopted was that known as the descending dose technic. In other words, the unit was determined by giving a series of rats, usually a very small number, decreasing quantities of the substance to be assayed, and finding that quantity which would just give the estrous reaction. Practically the whole of the chemical work prior to 1927 depended upon this method of standardization. The results of purification differed very greatly in the various laboratories in America and Europe. Some workers claimed to have produced a unit of very low weight, while others hotly contested this and said that they were unable to confirm these investigations. Some worked with aqueous solutions of the hormone and others with oily preparations, and many workers regarded the water-soluble preparations of their colleagues as

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being completely inactive. As an example of this may be quoted the opinions of Frank<sup>1</sup> in his recent book on the subject. It would appear at first sight impossible to find any explanation for this great divergence of views with regard to the potency of the various preparations, and it is with the elucidation of this problem that I particularly wish to deal. In the first place, it can be conclusively proved that aqueous and oily solutions must be considered entirely separately, and that the same rules for standardization cannot be applied to both. Before going into this in detail, however, it would be advisable to discuss the elements of standardization technic employed in this type of method. Recent research on hormone standardization, and also the standardization of drugs by biologic methods, has emphasized the great importance of the individual variability of the test animals. We are all familiar with the various stages passed through in the production of a uniform

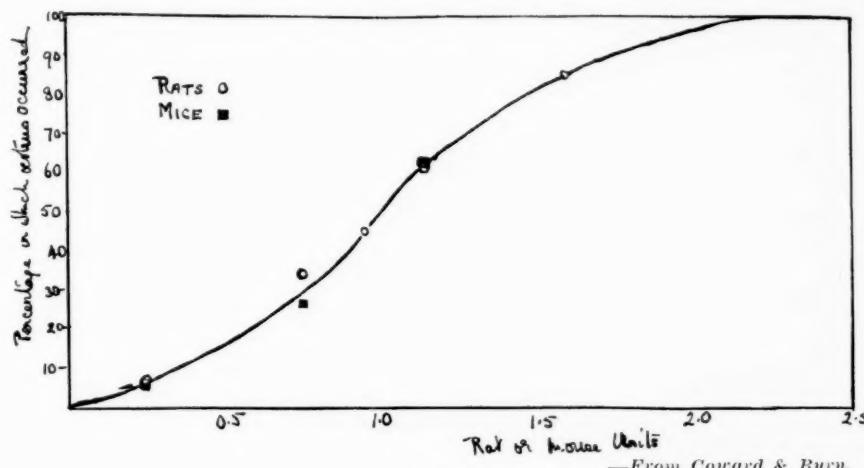


Fig. 1. —From Coward & Burn.

strength of insulin. In the early days, very few animals were used and it was assumed by most workers that starved rabbits of the same weight reacted quantitatively the same to the same doses of insulin. The error of this supposition was quickly brought home to the investigators, and now the elaborate statistical methods, such as those advocated by the League of Nations Committee, have to be employed. Precisely the same facts govern the standardization of estrin. Undoubtedly the work of Coward and Burn in 1927<sup>2</sup> was responsible for changing the whole of the outlook on this problem. These workers showed that if a large number of ovariectomized rats, nearly 100, were all given the same quantity of estrin, only a certain number of them reacted. Thus, with the particular dose tried only half of them gave a positive result, and these workers then showed that if more of the substance was given, an increasingly high percentage of animals showed a positive response, and they were thus able to plot out a curve (Fig. 1).

Here it can be seen that a curve of a sigmoid type is produced, and the very fact of the existence of this type of response puts out of court quite definitely the possibility of ever being able to use a descending dose method of standardization. In fact, the employment of this type of method can yield results which will be some hundreds of per cent, inaccurate. As soon as this paper was published the work was repeated in my laboratory, and was definitely confirmed. It became obvious that by this means it was possible to account for some of the grave divergencies between the individual workers. It can be seen from the shape of the curve that the slope is steepest in the region where 50 per cent of the animals showed a positive response, and Coward and Burn proposed a definition of the unit as that amount of material capable of producing estrus in 50 per cent of a series of animals of not less than twenty in number which had all been injected with the same amount of hormone. In our subsequent experiments this type of method was adopted, and it has also been adopted by other workers. Thus Laqueur<sup>3</sup> employs a similar method, but makes the unit that amount of material which produces a positive response in 75 per cent of the animals.

While confirming the main points of Coward and Burn's publication, we were not able to concur with two of their conclusions; namely, that the rat and mouse units were the same, and that the distribution of the material in a series of injections does not increase the potency. It is easy to find an explanation for the latter, since the material used by Coward and Burn was a relatively impure oily preparation which was very slowly absorbed. Later work with a highly purified preparation showed that this contention is incorrect. Turning to the type of preparation employed, it will be remembered that it was stated earlier that entirely different rules must be laid down for the standardization of water-soluble preparation. Failure to recognize this fact has led to many misunderstandings. For example, Coward and Burn employed single injections, Allen and Doisy in their original work employed three injections at four-hour intervals during the first twelve hours, and Laqueur used six injections spread over two and a half days. Now it must be remembered that the material prepared by Laqueur is a highly active, water-soluble hormone, but if his or any similar preparation be tested by the method of Coward and Burn, or by that of Allen and Doisy, an entirely negative result will be obtained unless very much greater doses be given than the units referred to by Laqueur. The importance of this fact was borne in upon us in a rather interesting manner. In 1926, attempts were made in my laboratory to prepare an estrus-producing hormone in a water-soluble form. We began with an oily material prepared in a manner similar to that described by Allen and Doisy, and a large bulk of this material was made and standardized and found to be active. Attempts were then made to hydrolyze the product by boiling with alkalies. Owing to the ease with which it

could be removed, barium hydroxide was employed, and a rough description of the method is as follows:

The oily material is boiled with baryta until no more was absorbed, in other words complete saponification was produced by adding successive quantities of baryta. At this stage the precipitate barium soaps and fatty acids were filtered off and the excess of barium hydroxide was precipitated by careful neutralization with sulphuric acid. A clear watery solution resulted which, when injected into animals in a single dose, proved to be completely inactive. At first we attributed this to destruction of activity by the boiling alkalies, and a great deal of work was done in an attempt to produce a preparation free from the associated fats. It appeared from other work which was in progress that the hormone itself was capable of withstanding the treatment already mentioned, and that destruction

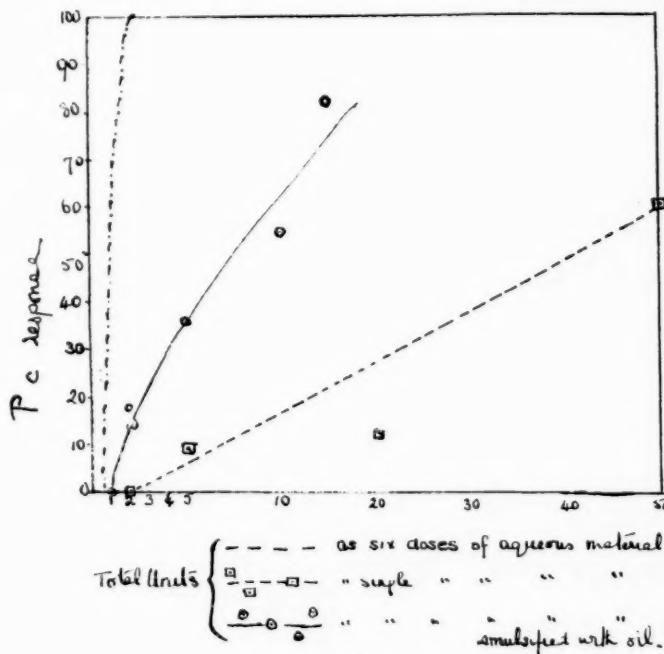


Fig. 2.

could not have occurred, yet we were faced with the fact that when injected the watery solution was inactive. It then occurred to us that perhaps the properties of the water-soluble material were different, as maintained by Laqueur, from a physiologic point of view from those of the oily material. Professor Laqueur, of Amsterdam, very kindly supplied us with some of his material, and on testing it by his method we were able to confirm the activity published by him. On the other hand, if this highly active solution were injected in one dose in the manner employed by us and others for the standardization of the oily materials, then a negative response was given. A repetition of this experiment with our own material produced identical results; namely, that it was inactive when given in one dose, but highly active when given by some method of divided doses, such as that described by Laqueur.

Here, then, lies a second difficulty in standardization. At first sight it is very difficult to explain these results, but it would appear reason-

able to account for them by postulating a very rapid excretion of the highly purified water-soluble material. When given in one dose this would produce no effect, owing to its rapid elimination, but when given in, say, six injections spread over three days, a summation of the stimuli would result and the material would appear to be highly active. There can be no doubt about the truth of these observations since in addition to the early work in Laqueur's laboratory and later in my own, it has been confirmed by Marrian and Parkes, and others. Any method for an accurate standardization must, therefore, concern itself first with the number of animals used; second, they must all be given the same dose and the results worked out statistically, and third, if the material is water-soluble the dose must be distributed in some particular man-

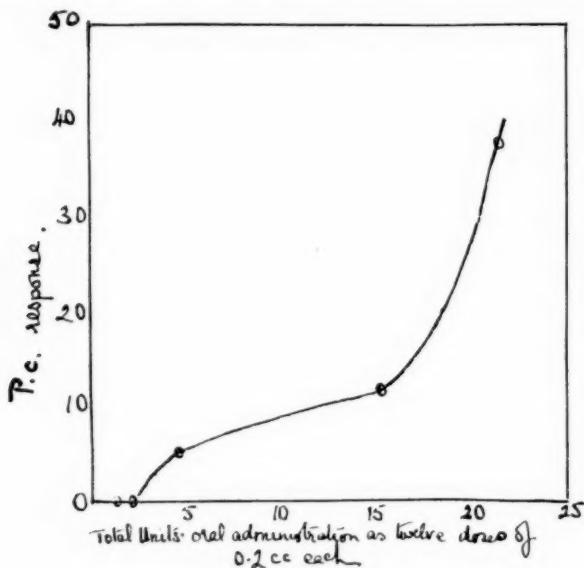


Fig. 3.

ner. It also follows that since an oily and impure solution will produce estrus in a single dose, and a highly purified, water-soluble material will produce estrus only when given in divided doses, there must be some intermediate stage of purity at which intermediate results will be obtained. This is well shown in Fig. 2.

Here can be seen the result of giving the same material first as six doses; second, as a single dose, and third, a single dose of aqueous material emulsified with oil. The six-dose-method produced a very steep curve, while the one emulsified in oil gave a much more sloping one, and the single dose produced the least response of all, indicating that 40 units of this particular material had to be given to produce 50 per cent response. It follows, therefore, that the administration of the hormone plays a very big part in its standardization, and that before the methods of one laboratory can be compared with those of

another a definition of the technie must take place. As pointed out by Laqueur, all these differences can be overcome if an international standard similar to that used in insulin be adopted. It is to be hoped that this will be done in the near future.

*Oral Administration.*—Most workers maintain that the hormone is inactive when given by mouth, or in any case is so slightly active that the possibility of its administration clinically in this manner can be disregarded. In Germany various relations have been given between the subcutaneous and the oral dose. Thus, some workers maintain that five times the subcutaneous dose will produce estrus when given orally, while others state that several hundred units must be given. It occurred to us that perhaps the same factors governed both oral administration and subcutaneous injection. Thus, it was felt that if a divided dose were given similar to the method advocated for the standardization of the aqueous material, it might be possible to produce estrus with very much smaller amounts than described by some workers. The curve shown in Fig. 3 illustrates this fact.

The material was administered to the animals in 12 doses of 0.2 c.c. each distributed over a period of three days, and it can be seen that the type of curve obtained is similar to that given by the subcutaneous method. By projecting the curve further than we have done, it would appear that about 30 units would be required to produce a response in 50 per cent of animals. It must be remembered, however, that this material was a highly purified water-soluble substance, and that the possibility of employing a cruder material with advantage for oral administration did not occur to us. This is described in a paper by Schoeller, Hohlweg and Dorn,<sup>6</sup> and they prove conclusively that the purity of the sample bears a direct relationship to the amount which has to be given to produce estrus by mouth. Table I is compiled from their paper.

TABLE I

MOUSE UNITS PER G.	NO. OF UNITS REQUIRED TO PRODUCE ESTRUS IN 50% OF ANIMALS WHEN ADMINISTERED ORALLY
8,000,000 (crystalline)	58
1,000,000	30
200,000	6

With a material containing certain lipoids they claim to produce a substance with which five times the subcutaneous unit will produce estrus in a similar number of animals. I have repeated their experiments, and confirmed their conclusions. It can be seen that all these facts have a distinct bearing on the clinical use of the estrus-producing hormone. On reviewing the lessons gained from the study of animal physiology it would appear that if subcutaneous administration is to be undertaken, the material must be given at frequent intervals in suc-

cessive small quantities. The purer the preparation, then the more frequently will it have to be given to take advantage of the full potency. On the other hand, if administration by mouth is to be undertaken, a cruder preparation containing protective lipoids must be employed.

#### CLINICAL EXPERIMENTS WITH THE ESTRUS-PRODUCING HORMONE

Before considering the results of administering the hormone to patients it is advisable to consider what results are likely to be anticipated from its use. It is indeed difficult to forecast the action of a substance, such as the estrus-producing hormone, since the biologic significance of menstruation is not agreed upon. It is known that this substance will produce estrus in the ovariectomized animal, but since it is not known to which particular part of menstruation the estrus cycle corresponds, it follows that the action of the hormone will be entirely problematic. Again, one is faced with the quantitative difficulty of how much of the material will have to be administered to women to produce an effect. It will be remembered that Coward and Burn state that the rat and mouse units are the same, but at least for aqueous material this is definitely not the case. Various workers postulate different relationships between the rat and mouse units from equality to 1:20. This discrepancy can doubtless be explained on the grounds discussed before; namely, the variations between watery and oily material, mode of injection, time of smearing, etc. We have been able to compare the rat unit as employed in our laboratory with the mouse unit as employed in Dr. Parkes' laboratory at University College, London. A careful series of crossover experiments showed that the relationship was exactly 1:10. As this is in proportion to the body weight, the rat being roughly 10 times as heavy as the mouse, it would appear that a kilogram basis for calculating the dose would be applicable. Arguing on the same basis, it would appear that 300 rat units would be required to produce a physiologic effect on a woman of average weight. If, however, structural uterine changes are required, then many times more units would have to be employed, for Parkes has shown that to produce uterine changes in the mouse as much as 300 units are required. In view, however, of the fact that the dosage can be spread out by injection, it is possible to get many hundreds of units injected subcutaneously in the course of a few weeks, and it is perhaps reasonable to suppose that by injecting say from 10 to 20 units a day for some prolonged period the result might be obtained. The following is an account of the investigations performed in my department:

The patients were transferred to us from the gynecologic out-patient department, where they had been subjected to a careful pelvic examination, and from our point of view they could best be considered under the following headings:

1. Patients with amenorrhea; these for the sake of convenience may be divided into two classes: the unmarried and the married. These groups correspond roughly to primary and secondary amenorrhea respectively.
2. Patients from whom both ovaries had been removed.
3. Patients in whom attempts were made to induce labor.
4. Patients at the menopause.

In Table II will be found the results of the treatment of all the patients who were injected with the hormone. Every patient to whom the substance was given has been included, so that there can be no question of any attempt at selection. In all, 78 patients with amenorrhea have been injected, and 16 of these were unable for various reasons to continue treatment. The results in these 16 have not been noted, as it was felt that their inclusion would be misleading. We thought it advisable to consider the results under two main headings: first, the direct objective result—namely, the establishment of menstruation—and secondly, the effect of the substance upon the general health and spirits of the patient. While the former is a matter of fact and can be expressed in figures and percentages, the latter is very variable, and indeed, in our opinion, is of little or no value.

TABLE II. AMENORRHEA

	UNMARRIED	MARRIED
Patients treated	40	38
Patients having full two months' course	32	30
Patients in whom menstruation started	10	18
Patients feeling better	30	29

Table II shows that menstruation started in 10 of the 32 unmarried women and in 18 of the 30 married women. In the successful cases the periods usually commenced within a week or ten days after the treatment and consisted first of all of a very slight bleeding, but this amounted to a full period in some. The bleeding was followed after three or four weeks by a full period, described by the patient as perfectly normal. The periods continued for at least six months and these patients all felt a great improvement in their general health. It must be admitted, however, that those women in whom the periods did not appear also felt very much better. A series of experiments was conducted on some of these patients to control the psychologic effect of giving injections, and in many cases excellent effects were observed after normal saline injections when the patients thought they were receiving the active preparation. The general tonic effect appears, therefore, to be largely due to suggestion, possibly associated with the fact that the patient was coming every day to the hospital for treatment.

*Patients From Whom Both Ovaries Had Been Removed.*—Four patients were treated. From the first, aged twenty-nine years, both

ovaries had been removed on account of cystic disease, and the uterus had been left untouched. The patient was seen five months after operation and had not had any periods. After the standard treatment, menstruation appeared in three weeks, and was followed by another period one month later. In this case the injections were carried on for five months and the periods continued normally. Cessation of treatment, however, was followed by abrupt cessation of the menses. In another patient, aged thirty-two years, the ovaries had been removed three months previously and the patient was suffering from marked menopausal symptoms. The results obtained were similar to those in the first case. The remaining two patients had undergone complete hysterectomy, together with removal of the ovaries, and were suffering mainly from vasomotor symptoms. Their ages were thirty-five and thirty-eight respectively. In the former patient there was a definite leucoplakia vulvae. In both patients the vasomotor symptoms were controlled, and the local condition of the vulva in the first patient was greatly improved by three months' treatment. Unfortunately, sufficient material was not available to continue the treatment or to increase the dose.

*Attempts at Producing Premature Labor.*—Three patients were treated, and the results are described in detail. It will be seen that in only one was there any evidence that premature delivery had been effected.

**CASE 1.**—Primigravida, aged twenty-six years, expecting July 15, 1928. Induction for (?) placenta previa, associated with persistent vomiting.

July 7. 12:15 P.M. Injection 1 e.e. estrin.  
4:15 P.M. Injection 1 e.e. estrin.  
8:45 P.M. Injection 2 e.e. estrin.  
July 8. 12:15 A.M. Injection 2 e.e. estrin.  
A few weak pains during night.  
11:00 A.M. Injection 2.5 e.e. placental extract.  
3:00 P.M. Injection 5.0 e.e. placental extract.  
7:00 P.M. Injection 5.0 e.e. placental extract.  
July 10. 12:45 P.M. No pains; general anesthetic; bougie induction.  
July 12. 7:00 P.M. Onset of pains.  
July 14. 1:30 P.M. Normal delivery after a long labor assisted by potassium, bromide and chloral, morphia and scopolamine, and pituitrin when the head was on the perineum.

**CASE 2.**—Multigravida, aged twenty-five years, expecting September 15, 1928.

July 20. 3:00 P.M. Injection 5 e.e. estrin.  
7:00 P.M. Injection 5 e.e. estrin.  
11:25 P.M. Onset of pains.  
12:00 P.M. Cervix admitted two fingers.  
July 22. 8:00 P.M. Dilatation 2/6.  
July 23. 7:45 A.M. Dilatation 5/6.  
5:15 P.M. Normal delivery, binovular twins, after morphia and scopolamine.

CASE 3.—Multigravida, aged twenty-two years, expecting May 12, 1928. Induction for (?) postmaturity and disproportion.

July 21.	3:00 P.M.	Injection 5 e.e. estrin.
	7:00 P.M.	Injection 5 e.e. estrin.
	11:00 P.M.	Injection 5 e.e. estrin.
July 22.	3:45 A.M.	Injection 5 e.e. estrin.
	3:30 P.M.	Injection 10 e.e. estrin.
	7:30 P.M.	Injection 10 e.e. estrin.
	10:30 P.M.	Injection 10 e.e. estrin.
July 23.	3:30 A.M.	Injection 10 e.e. estrin.
July 25.	12:30 P.M.	No pains; external cephalic version; bougie induction.
July 26.	4:50 P.M.	Onset of pains.
July 28.	5:20 A.M.	Normal delivery.

We came to the conclusion that very much larger doses of the material would have to be employed before definite results could be expected; and, as at this time we heard that a more elaborate series of experiments was in progress elsewhere, we decided to abandon the investigation.

*Administration During Menopause.*—A series of five cases was treated by daily injections of 10 units of the hormone, and in all there was a marked improvement. It was found that the extract possessed definite powers of controlling the vasomotor and general symptoms of nervous irritability, but the number of cases was too few to produce anything definite.

Observations made on the possibility of giving the material by mouth open up further research on this subject. A series of patients are being treated by us with an oral preparation of which it is known that five times the subcutaneous unit correspond to one oral unit. At present it is too early to report any definite results, but it would appear that definite action may be obtained by this route.

#### THE ASCHHEIM-ZONDEK REACTION FOR PREGNANCY

The application of the excretion of sex hormones to the diagnosis of pregnancy has recently been made possible by the work of Aschheim and Zondek. It will be remembered that early in pregnancy estrin and an ovary-stimulating substance are excreted in the urine. The presence of the former is nonspecific and can occur in conditions other than pregnancy, but the latter appears, with very few exceptions, to be specific. The test depends upon injecting the urine, or a detoxicated preparation of it, into immature female mice and noticing whether corpora lutea and corpora hemorrhagica (Blutpunkte) are produced. A very high percentage of accuracy is claimed by Aschheim and Zondek in both pregnant and nonpregnant women. The technic has been described in a number of places and hence it is not necessary to say anything about it here. The results obtained in my department are shown in Tables III and IV.

As can be seen, very few mistakes were made and only one specimen from total of 208 gave an incorrect positive response. The patient was a woman forty-six years of age at the menopause who presented no peculiarities. The test was repeated on two different specimens of urine, one of which gave a very feeble positive response in one out of five mice, while the second specimen was negative. A further specimen was obtained and a positive reaction resulted. It is

TABLE III

SPECIMENS	CASES	TEST POSITIVE	TEST NEGATIVE	PER CENT ERROR
Females definitely known—				
(a) to be pregnant	126	122	4	3.2
(b) not to be pregnant	82	1	81	1.2
Males	6	0	6	—

TABLE IV

CONDITION	CASES	TEST POSITIVE	TEST NEGATIVE
<i>Nonpregnant</i>			
Normal female—			
24 hours after delivery	1	1*	0
48 hours after delivery	1	0	1
Lactating	2	0	2
Menstruating	2	0	2
Young girl, 3 months	1	0	1
Young girl, 10 years	1	0	1
Ovarian tumor, benign	2	0	2
After abortion (4 days)	1	0	1
Menopause	5	1*	4
Various gynecologic conditions	5	0	5
Extreme obesity	1	0	1
Menorrhagia	1	0	1
Pituitary tumor	4	0	4
Fibroid of uterus	1	0	1
Total	28	2	26
<i>Pregnant</i>			
Normal female 1½ hour before delivery	1	1	0
Pulmonary tubercle and pregnancy	1	1	—
Total	2	2	—

\*Weak.

difficult to understand the explanation of this, as all other patients at the menopause gave no evidence of a positive reaction. As Fluhmann has shown, castration results in an increase in the amount of anterior pituitary hormone in the patient's blood, and it may be that the cessation of ovarian function at the menopause caused a like phenomenon in this patient.

Out of 126 pregnant women only 4 showed negative tests. One of these miscarried three weeks after the test, but the remaining 3 went to term in the ordinary way. The specimens were nontoxic and, in so far as is known, nothing abnormal occurred in the course of the reaction.

With regard to the date at which the reaction first becomes positive, it is stated by most workers that this occurs at the fifth week. The earliest case in our experience was one in which the reaction was positive when the expected period was only nine days overdue.

It is also interesting to note the very rapid disappearance of the hormone from the urine after delivery. Thus, within forty-eight hours, as shown in Table IV, a negative response was obtained. Care was taken to exclude other possibilities, such as the onset and cessation of menstruation and the early months of puberty in which, presumably, there is a large amount of the hormone present in the body. No positive reactions were found.

Attempts have been made to apply this test to the study of disorders of the internal secreting glands. Thus, a number of patients with tumors of the pituitary gland have been investigated. In all of these the diagnosis was confirmed first by x-rays and then by exploratory operation. Up to the present time four such cases have been examined and in none was the reaction positive.

It would appear, therefore, that the test is very specific indeed. At present it is used as a routine in the department, and the gynecologic department requests a large number of tests per week for both in- and out-patients. We also find that the reaction is very useful in the general medical and surgical wards. Great care is required in the organization to have a series of mice of the right age growing up in successive weekly batches so that the tests are never held up.

#### CONCLUSIONS

In conclusion it would appear that a study of the physiology of the sex hormones offers one of the most promising fields in combined clinical and academic research. Out of the purely academic work has evolved a reaction of such practical value as the Aschheim-Zondek test for pregnancy. New preparations are constantly being obtained; as, for example, the work of Corner in relation to the corpus luteum or progestational hormone and, finally, the various fractions obtained from the anterior lobe of the pituitary. The clinical possibilities of these substances are very great indeed, and it will be interesting to watch their future developments.

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## THE MORPHOLOGY OF MENSTRUAL BLOOD AND ITS DIAGNOSTIC VALUE\*

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Sinai Hospital)

**I**N PREVIOUS papers published in 1929, it was noted that the normal menstrual discharge contained definite morphologic elements. The recognition of these elements enables us to identify the fluid containing them as menstrual blood, thus differentiating it from other hemorrhagic vaginal discharges.

It had been pointed out by other investigators that uterine mucosa could be found in the menstrual discharge. This fact was utilized to substantiate the contention that there was a desquamation of the uterine mucosa during menstruation, but these findings were not employed as a means of identifying a given hemorrhagic discharge as menstrual.

Clinically it is of extreme importance to differentiate conditions associated with bleeding from the genital tract. Previous to the above-mentioned papers published in 1929, there was no definite method available to make this differentiation other than by the gross appearance or the nonclotting characteristic of the menstrual blood. These criteria, however, were so variable that as an accurate method of differentiation they were not of very great assistance.

Our previously published series of 200 cases has been more than doubled and the findings in this larger series corroborate the earlier published results.

In the menstrual blood (Table I) there is a definite variation in the quantitative content of uterine epithelium. It is found in most marked profusion on the second day of the period. On the first and third days the percentage of positive findings is not so high, while on subsequent days mucosa is only occasionally present.

TABLE I. SHOWING PERCENTAGE VARIATION OF UTERINE VAGINAL ELEMENTS ON  
SUCCESSIONAL MENSTRUAL DAYS

	FIRST DAY PER CENT	SECOND DAY PER CENT	THIRD DAY PER CENT	FOURTH DAY PER CENT
Uterine epithelium	50	74	25	3
Uterine stroma	75	90	91	4
Vaginal spindles	95	95	82	100
Vaginal plaques	50	72	55	25

\*Read at the Fifty-sixth Annual Meeting of the American Gynecological Society  
Hot Springs, Va., May 18-20, 1931.

Apparently the desquamation of the uterine epithelium begins just before the appearance of the menstrual bleeding and in spite of the fact that fragments of mucosa are found in only about 50 per cent of the cases on the first day, undoubtedly they are present in all specimens. This discrepancy may be due, in the first place, to the scanty amount actually present on the first day, and in the second place, to the limited quantity of material available for examination. If the entire menstrual discharge for the first twenty-four hours were subjected to histologic examination, undoubtedly mucosal fragments could be identified in every case. On the second day a percentage rise occurs, probably due to the fact that the desquamation is more extensive and the fragments more readily encountered. On the third

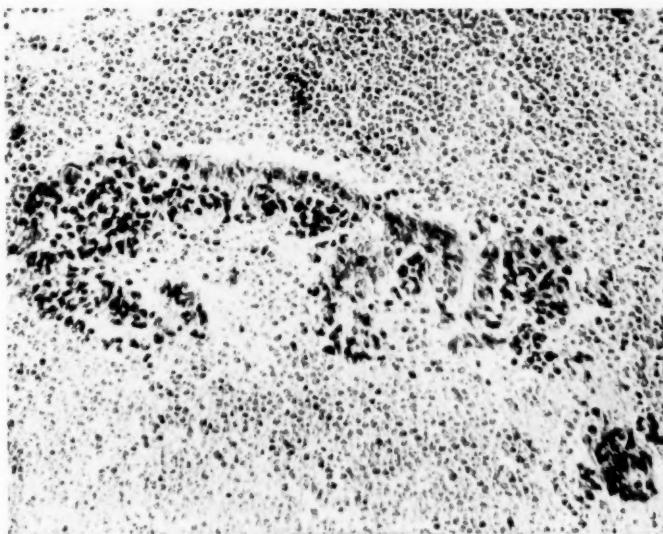


Fig. 1.—Strip of surface epithelium with a small amount of underlying stroma and a small stromal clump in the right lower corner. Sufficient to warrant the diagnosis of menstrual blood.

day the peak of the desquamation has apparently been passed and consistently the percentage of positive findings begins to drop.

As mentioned before on days subsequent to the third, only occasionally is epithelium identified, this in all likelihood being due to the initiation of the reparative process at this time and the absence of further desquamation. In addition, the flow of blood on the previous days has already washed loose and carried out all the previously desquamated epithelial fragments.

In Fig. 1 is illustrated a type of mucosal fragments not uncommonly encountered, representing a strip of surface epithelium with a small amount of underlying stroma. At other times larger fragments of mucosa containing glands and stroma could be identified. (Fig. 2.)

The nuclei show pyknosis, the glandular and surface epithelium is collapsed and compressed and evidences a lack of secretory activity. Occasionally large plaques of mucosa with well preserved epithelium

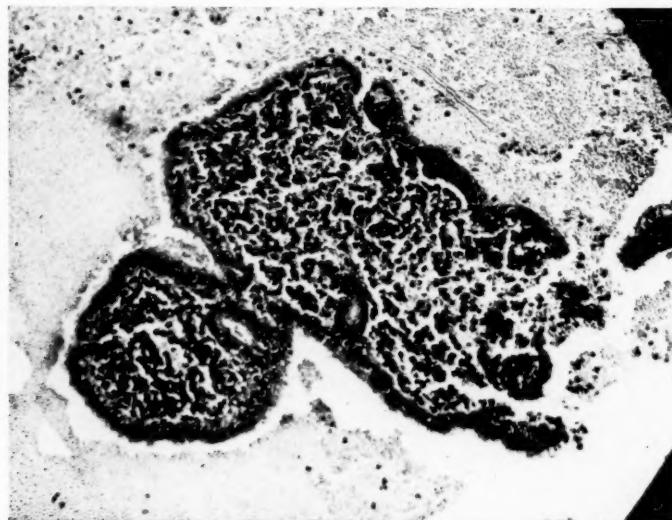


Fig. 2.—Large fragment of mucosa showing epithelium and glands with marked pyknosis of the nuclei. Sufficient to warrant the diagnosis of menstrual blood.

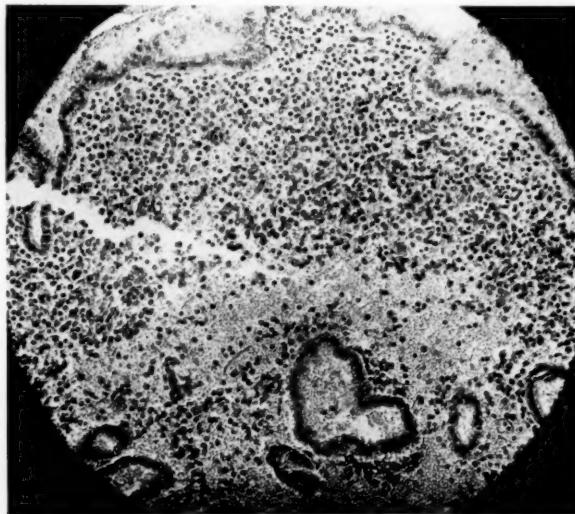


Fig. 3.—Large plaque of mucosa with well preserved epithelium both on the surface and in the glands showing decidual like reaction in the stroma.

both on the surface and in the glands, and containing stroma with a decidual like reaction have been encountered. (Fig. 3.) This tissue resembles fragments extruded in cases of membranous dysmenorrhea. In many instances material comparable to that described has been

found without the associated pain of dysmenorrhea. It might too be of interest to point out that in these fragments there is evidence of secretory activity and further study and investigation of this phenomenon might possibly aid in adding to our knowledge of the etiology of dysmenorrhea.

Stroma cells were found even more frequently than epithelial fragments and often independent of them. The extrusion of stromal fragments also showed time variations. They were more commonly found on the second and third days of the period. As a matter of fact on the second day they were found in 90 per cent of the cases and on the third day in 91 per cent. This high incident of positive findings

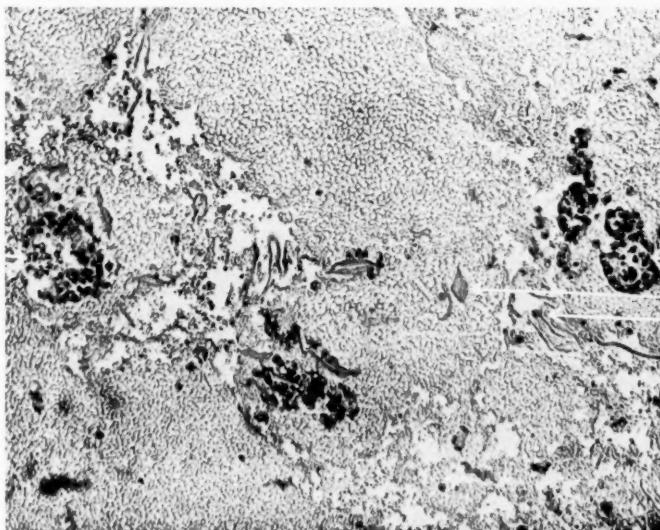


Fig. 4.—Several small stromal clumps of well preserved cells. Sufficient to warrant the identification of the fluid as menstrual blood.

was followed by a very sharp drop on the fourth day. These stromal fragments presented a definite entity in the menstrual blood though in some instances only one or two tiny clumps could be found in each slide. These clumps, when present, are sufficiently characteristic to warrant the identification of the fluid in each they were contained as menstrual blood.

In Fig. 4 we can identify several small clumps of stroma composed of well preserved cells, which finding is sufficient to warrant the identification of the medium in which they were contained as menstrual blood. These stroma clumps occur as small groups of darkly stained cells, sometimes very few in number, occasionally in masses of twenty or thirty cells. The nuclei at times appear normal and at other times show pyknosis or other evidences of degeneration. (Chart 1.)

In a small percentage (9 per cent) of cases neither uterine epithelium nor stroma were found. This discrepancy might be accounted for by the fact that not sufficient material was examined or that in certain individuals desquamation of uterine epithelium does not occur. This latter condition has been shown by Heape and Corner to take place in the monkey.

In addition to the presence of uterine epithelium and stroma, vaginal epithelium is found in practically every specimen of menstrual blood examined.

It occurs either as individual cells (Chart 2), few in number or in great profusion, or as vaginal plaques of varying types made up of cell

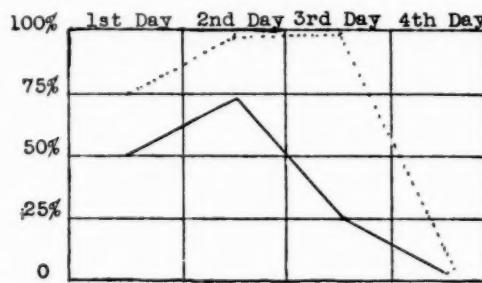


Chart 1.—Graph showing percentage variations in uterine and stromal elements in menstrual blood on successive days. Dotted line represents stroma. Solid line represents epithelium.

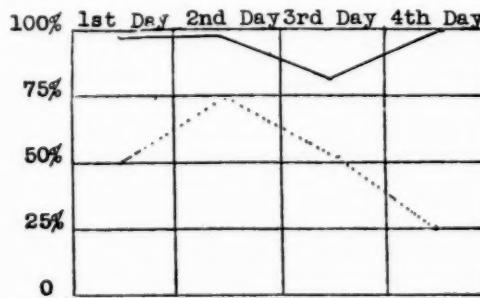


Chart 2.—Graph showing variation in occurrence of vaginal mucosa in menstrual blood. Dotted line represents vaginal spindles.

masses of one hundred or more cells arranged in layers. In association with the other morphologic elements, the presence of these vaginal elements makes the diagnosis of menstrual blood as distinguished from other hemorrhagic fluids more definite. This desquamation adds additional confirmation to the contention of Dieck and others that in the vaginal mucosa a cyclical destruction and repair takes place in keeping with the ovarian and uterine cycle. Figs. 5, 6, 7, and 8 illustrate the varying types of vaginal desquamation encountered in the menstrual blood.

We have studied a large number of cases with irregular vaginal bleeding clinically nonmenstrual in type. They constituted various

types of gynecologic cases associated with fundal bleeding. In about 10 per cent of the specimens examined uterine epithelium or stroma or both were present. However, closer study of the histories of the cases with positive findings made it apparent that we were dealing

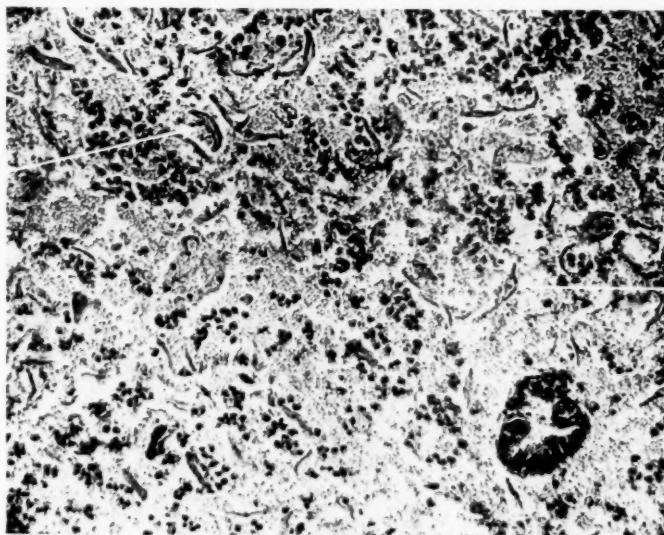


Fig. 5.—Mass of isolated spindle cells derived from the vagina in addition to one small uterine gland.

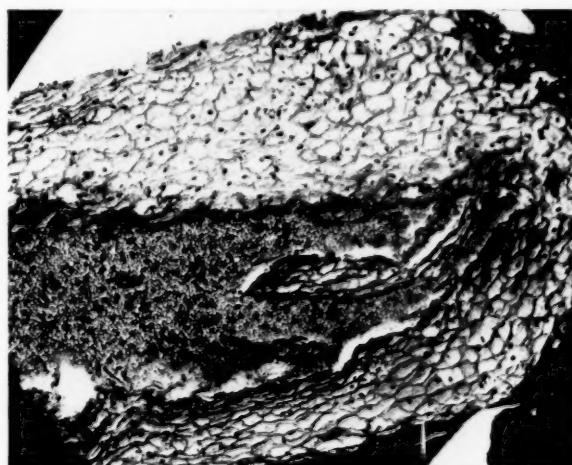


Fig. 6.—A large fragment of vaginal mucosa. Such large masses are not common findings.

in all probability with menstrual blood in these instances. For example in one case the history suggested the possibility of an ectopic pregnancy, but an exploratory curettage done one day after the vaginal blood was obtained for examination, showed uterine mucosa in

the normal menstrual phase. In two other cases the bleeding occurred approximately one month after a miscarriage. One may be justified in interpreting such an episode of bleeding as menstrual. It is not necessary to go into the details of the other seven histories, but in

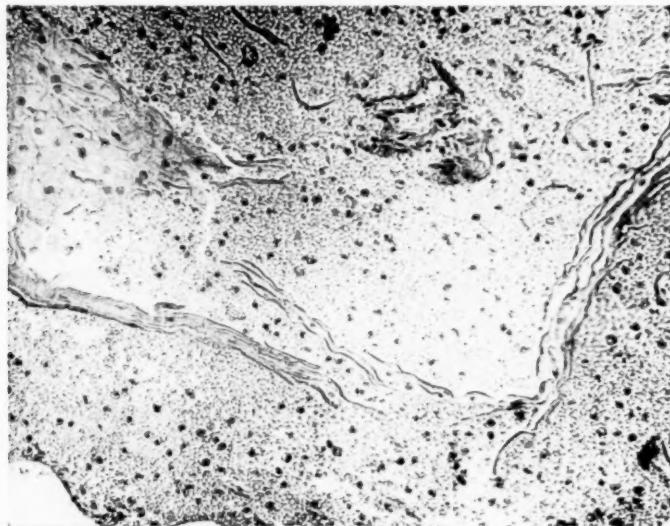


Fig. 7.—Strips of cornified epithelium with numerous isolated and vaginal spindles.

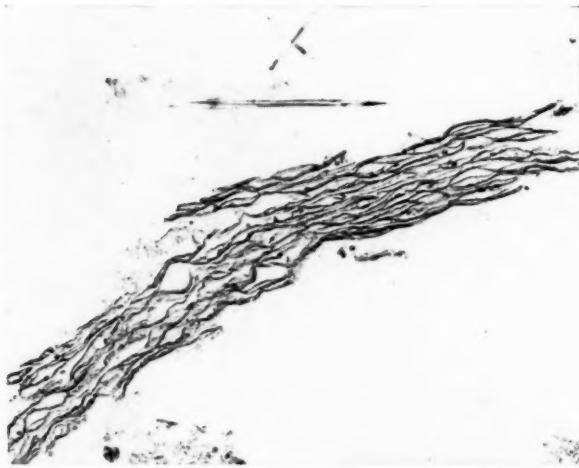


Fig. 8.—Vaginal plaques representing the most superficial layers of the vagina.

each instance sufficient evidence was obtained to make us believe that the cases presenting uterine elements in the blood were probably menstrual.

It happens not infrequently that we are confronted with a clinical case associated with bleeding, the nature of the bleeding being diffi-

cult to determine. The proper interpretation of the type or the etiology of the hemorrhagic discharge will facilitate an accurate diagnosis. By subjecting such cases associated with a hemorrhagic vaginal discharge to an examination, as above described, we were able, in many instances, to aid ourselves in the clinical differentiation.

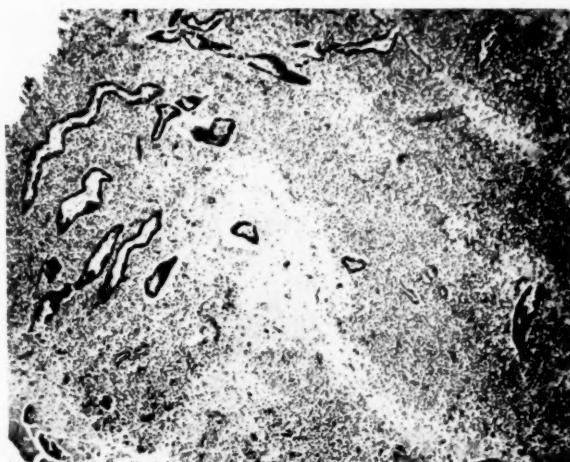


Fig. 9.—Mucosal desquamation. Uterine mucosa typical of menstruation from a case of suspected tubal pregnancy.



Fig. 10.—Fragment of decidua found in vaginal blood in a case of tubal pregnancy.

In several instances where an ectopic pregnancy was suspected the finding of typical menstrual fragments (Fig. 9) made it evident that we were dealing with a delayed period, associated with some abdominal condition giving rise to right or left side pain, and not with an ectopic pregnancy. It is understandable that one might expect to find in the hemorrhagic discharge associated with an ectopic preg-

nancy, fragments of decidua which represent the disintegration of the uterine mucosa. However, our experience has resulted in the failure to identify tissue that could be confused with the typical uterine desquamation of menstruation.

In another patient in whom an ectopic pregnancy was suspected, the hemorrhagic vaginal discharge contained fragments of typical decidual tissue (Fig. 10). This tissue was in no way to be confused with the uterine desquamation characteristic of menstruation. The only possible confusion would be with a case of membranous dysmenorrhea which clinically in this instance could be excluded. The differentiation from pregnancy could be made because of the absence of typical pregnancy glands, and we therefore felt that the diagnosis of an ectopic pregnancy was justified. The diagnosis was confirmed by laparotomy.

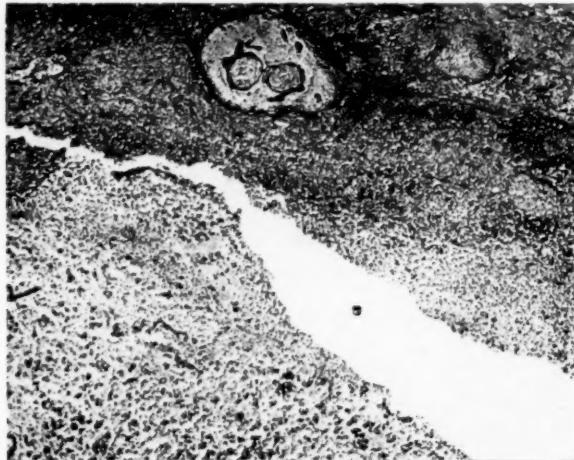


Fig. 11.—Tissue obtained from a case of incomplete abortion showing typical chorionic villi.

Another case of interest was one where the diagnosis between an abortion and an ectopic pregnancy could not be determined. Examination of the vaginal blood showed the presence of two well preserved chorionic villi (Fig. 11) which, of course, immediately established the diagnosis.

In three instances of prolonged secondary amenorrhea, in one case of three years' duration the onset of bleeding was the cause of great concern to the patient and it was important if possible to determine the nature of the bleeding. In these cases the vaginal discharge contained uterine mucosal desquamation such as is found in normal menstrual blood (Fig. 12). This finding established the fact that we were dealing with a typical menstrual period after a prolonged amenorrhea. In another instance of secondary amenorrhea of two years' duration

there occurred a moderate vaginal bleeding after six injections of Theelin. In the vaginal hemorrhagic discharge uterine mucosal fragments were present (Fig. 13) identifying the discharge as menstrual. We cannot, however, ascribe to the administration of Theelin the pri-

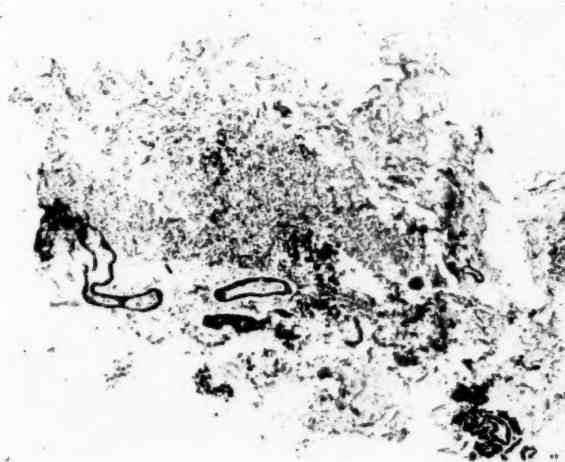


Fig. 12.—Typical fragment of uterine mucosa sufficient for the diagnosis of menstrual blood.

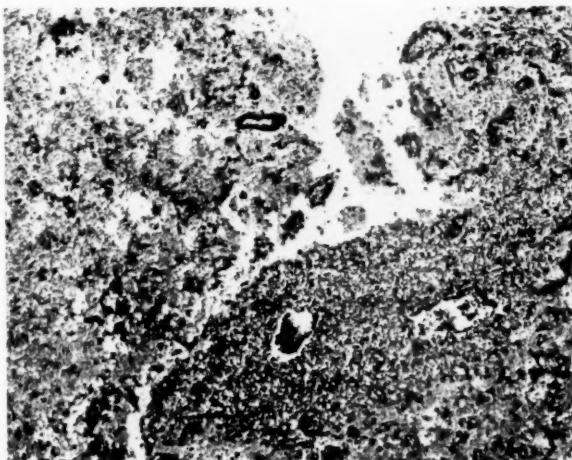


Fig. 13.—Typical fragments of uterine mucosa sufficient for the diagnosis of menstrual blood.

mary rôle but we have established a method of determining whether the hemorrhagic discharge following medication, after a period of amenorrhea, is menstrual or not.

In some instances of fibroids associated with polymenorrhea it was possible to show that many of the episodes of bleeding were not due

to the pressure of the tumor or an erosion of the uterine mucosa but to a regular menstrual period in the course of the bleeding associated with fibroids.

It is interesting to note that in cases of functional bleeding both at puberty and in more mature women uterine epithelium is found in the hemorrhagic discharge only occasionally. Of course, it might be present in the very first few days but in these instances where material was obtained at the beginning of a known metrorrhagia we were unable to find mucosal fragments. This leads to the possible assumption that the bleeding associated with these functional cases is not accompanied by a desquamation of the mucosa and probably has a mechanism that differs from that of the normal menstrual flow. Of course, during the menstrual period in the course of a functional metrorrhagia mucosal elements might be present.

To conclude then we can state that we have at hand a means of identifying the true menstrual discharge in about 90 per cent of the cases and at the same time a method that will frequently aid in the differentiation between menstrual bleeding and other types of hemorrhagic vaginal discharge.

100 EAST SEVENTY-FOURTH STREET.

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**Pratt and Smeltzer: Nasal Spray Method of Administering Hormones of the Ovary and Pituitary Gland.** *Endocrinology* 13: 320, 1929.

After experimenting with rats and mice, Pratt and Smeltzer decided that the nasal mucous membrane could be used satisfactorily for the absorption of extracts of the ovary and pituitary gland. Estrus was produced in spayed rats when the nasal cavity was sprayed with ovarian hormone. It required twice the amount used in the nose to produce estrus if the solution was applied to the vaginal mucosa. Several case reports are cited by the authors to show the efficiency of the method in woman. Results were obtained with both ovarian and pituitary extracts. Irritation of the nasal mucosa was not produced but coryza and other local abnormalities are contraindications.

W. KERWIN.

**Ford, F. A.: Treatment by Roentgen Rays in Ovarian Dysfunction.** *Minn. Med.* 13: 186, 1930.

In discussing irradiation of pituitary and ovaries in amenorrhea, oligomenorrhea, menorrhagia, metrorrhagia, and dysmenorrhea, 6 cases are presented in which there was improvement or cure following treatment. Such results, however, can be obtained in only 50 per cent of cases.

FRANK SPIELMAN.

## RERADIATIONS IN THE RADIUM THERAPY OF CARCINOMA OF THE CERVIX UTERI\*

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THE effect produced by the action of radium upon malignant or normal cells should be known to all who use this element. Radium does not remove a cancerous growth by destruction of the entire part affected, as is accomplished by surgery or cautery, but the gamma rays have a direct selective action on the cancer cells, destroying them without injuring the normal cells around the site of the neoplasm. This is often demonstrated in healed cases of carcinoma of the cervix where the normal shape of that organ may be restored with no trace of the cancerous growth.

Another action of radium is to induce a proliferation of connective tissue. The connective tissue contracts with the resulting obliteration in great degree of the blood and lymph supply, producing the contracted, pale-looking cervix and funnel-shaped vaginal vault, that we see in the ideally healed cases.

Therefore we must appreciate that, if the dosage suitable for a certain case is used, we will destroy the cancer cells but not the normal tissues, owing to the selective action of the gamma rays on the carcinoma, and the greater resistance or toleration of the normal tissues.

It must be borne in mind, then, that if we give much larger doses of radium than are required to destroy the cancer cells, we shall also destroy the normal structures beyond repair and produce extensive necrosis with resulting septic absorption, hemorrhages, and injury of adjacent viscera, with perhaps the formation of fistulas.

These unfortunate results of overradiation with this powerful element are commonly attributed to the extension of the carcinoma, or frequently the action of the radium is blamed and consequently condemned as of no value. We must also see that if too small an amount of radium is used, or for too short a time, we may fail to destroy all the cancerous tissue.

The radiologist then must work between the two extremes of radiosensitivity of the cancer cells, on the one hand, and the normal tissues which are the seat of the disease, on the other. If he oversteps these bounds he produces either a so-called "primary acute radioneurosis" or does not cure the condition, owing to a failure to destroy all the neoplastic tissue.

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Regaud, Nogier, Delbet, Moequot, Herrenschmidt, and others have stated that if cancer cells are subjected to insufficient radiation to destroy them, these tissues become radioresistant and this resistance increases with subsequent, repeated, and prolonged treatments until the tissues become immune to the radium. The normal tissues also become sensitized.

Applications of radium that are prolonged, or repeated at too short intervals, may produce the so-called "late reaction" of radium which is not manifest for six months, or a year or more, following the initial treatment. Dense infiltration and pelvic pain with ulceration and discharge may develop, and it is apt to be attributed to a recurrence of the disease, when actually it is the result of overradiation of the tissues with resulting excess of connective tissue formation which produces a slowly developing obliterating arteritis. These devitalized structures ulcerate and become a ready prey to infection.

Therefore, it is not generally regarded as sound technic by most authorities to expose carcinomatous tissue to repeated radiations over long periods of time.

Schmitz states that following the initial treatment "should healing of the cancer not ensue, it is not advisable to retreat the patient" and says "he has never seen any benefit from such retreatment and on the contrary the tissues will not recover from the added damage. They become indurated and break down. Such radiation induration and ulcers form very slowly and rarely appear and cause symptoms before the expiration of a year or more."

Lacassagne says that this immunity to radiation on the part of the neoplastic tissue offers an explanation of the fact that epitheliomata of the cervix, which have recurred after radiotherapy, can rarely be cured. Their experience is only 4 cures out of 73 patients who had been previously radiated, or 5 per cent. Norris has expressed similar views.

In accordance with this view which generally prevails, the technic usually in vogue is to complete the treatment in a relatively short period of time, and should recurrences appear, to regard further radiotherapy as harmful and useless.

According to Lane-Claypon's report, the percentages of recurrences at different periods after treatment were 47.5 per cent during the first year, 36.2 per cent the second year, 11.8 per cent in the third year, and 4.5 per cent in the third to fifth year period. If nothing further is done in the way of treatment, 42.5 per cent of recurrences after the first year would be hopelessly lost.

In our clinic at the Woman's Hospital since 1920, we have followed a systematized method which we have previously published, the essentials being to build up the patient's resistance when indicated, by a blood transfusion, and the employment of a test dose of radium varying from 2,400 to 3,600 milligram hours. Occasionally, we have used as much as 4,200 milligram hours, depending on the size of the neoplasm.

We, then, two to three months later, carefully estimate the result. Subsequent radiations and the dosage are dependent on the reaction obtained with the test dose. A personal monthly follow-up is carried out throughout the five-year period of observation as far as it is possible to do so, and whenever we have discovered signs of a beginning recurrence that is within reach, we have not hesitated to employ re-radiation at any time throughout the five-year period of observation.

The outstanding feature of our method is this re-radiation whenever our monthly follow-up inspection reveals evidence of metastases in the vaginal tract. Nearly 50 per cent of our cases have had repeated radiations.

This is of interest because it is not the usual practice, on account of fear of the radioresistance of the tissues being increased by over-radiation and the resulting late radium necrosis. This danger in our belief occurs only if prolonged applications of a heavy dosage are used, and at too frequent intervals. This we try to avoid. Our employment of re-radiation is largely for metastatic outbreaks in the vaginal walls or fornices, and consists of a relatively small dosage, usually in the form of platinum needles containing 12 to 13 milligrams of element, although should the nature of the recurrence make the use of a contact-application more desirable, we do not hesitate to use tubes or flat containers. The average dose ranges from 300 to 1,200 milligram hours, depending on the size and location of the metastases.

Very few clinics have so frequent a follow-up, continued throughout the five years, and it is to this that we attribute our success in saving some cases by discovering recurrences long before the patient would be aware of any suspicious symptoms.

We have many instances of successful radiation of such metastases occurring two, three, and four years or longer after the initial treatment—our cure rate for 170 of these cases being 26.5 per cent. We are encouraged to continue this practice in spite of some criticism, as our results would seem to justify it, and as several authorities have recently reported the use of this procedure.

Heyman, in an address before the Royal Society of Medicine in 1929, states that, "we have in recent years, in cases of persistent small residua and in the cases of smaller vaginal recurrences, made use of intubation of radium needles." The Marie Curie Hospital of London reports that they give repeated radiations in certain cases with improvement. Taussig, in a discussion before the American Gynecological Society last year, spoke of the value of re-radiation, stating that he had caught recurrences in a very early stage and had been able to save and prolong life thereby.

In this connection it is interesting to note that in the Munich Clinic, the standard treatment is to give a second radiation eight weeks after the first, and if the follow-up shows it necessary, a further treatment is given after a two months' interval. This is re-radiation in principle,

according to our viewpoint. Voltz states that no case of theirs survived, that did not receive the second treatment two months after the first.

In an analysis of a series of 147 of our treated cases with both epidermoid and the adenocarcinomatous type of cell, in which we have complete records, reradiations were given in 75 cases at various times during the five-year period, or 51 per cent. Of these 75 radiated patients 18, or 24 per cent, lived five years or longer, and 16 lived from five to ten years. As an example of the value of repeated radiations, one patient with cells of Type II, now living and well seven years and five months after her initial treatment, had five reradiations, the last being twenty-two months ago.

It seems fair to assume that if this group of 75 patients with metastases had been abandoned without further radiation for fear of a late radium reaction, or that an acquired radioresistance would prevent further beneficial result from the radium, they would all have succumbed to the recurrent carcinoma.

The locations of the metastases in 54 patients who received reradiations were as follows:

- 45 in the cervical region
- 5 in the vaginal wall
- 2 in the base of the broad ligaments in the lateral vaginal fornices
- 1 in the vulva
- 1 in both cervix and vaginal wall

TABLE I. SHOWING THE AVERAGE LENGTH OF LIFE AFTER RECEIVING THE LAST RADIATION IN 111 CASES

Group	TYPE OF CELL	STANDARD TEST RADIATION	SUBSEQUENT RERADIATIONS				
			I	II	III	IV	V
I	Cases	15	12	5	1		
	Average Life Months	36	17	5.5	4		
	Living 5 Years	6	1				
II	Cases	16	9	3	2	1	
	Average Life Months	36	40	32.5	45		25.5
	Living 5 Years	4	2	1	1		1
III	Cases	8	6	2			
	Average Life Months	23	34	8			
	Living 5 Years	1	2				
I-II	Cases	7	4		1		
	Average Life Months	11	40		25		
	Living 5 Years	1					
I-III	Cases	4		1			
	Average Life Months	30		1			
	Living 5 Years						
II-III	Cases	2					
	Average Life Months	5.5					
	Living 5 Years						
Adeno- car- cinoma	Cases	2	6	3	1		
	Average Life Months	5.5	42	15	12		
	Living 5 Years	3	1	1	1		

Table I gives the average length of life after receiving the last reradiation in 111 cases, showing the results in relation to the type of cell.

Table II shows the average time of recurrence of carcinoma after various reradiations in a series of 57 cases of the epidermoid type of cell.

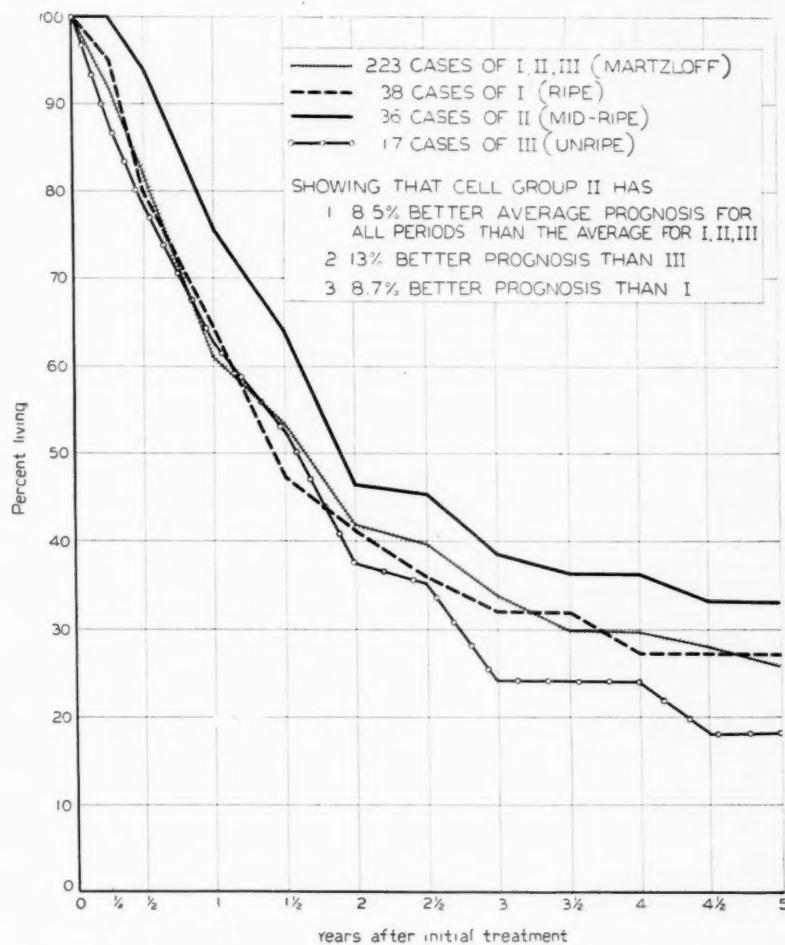


Fig. 1.

TABLE II. AVERAGE TIME OF RECURRENCE OF THE CARCINOMA AFTER THE VARIOUS RERADIATIONS IN 57 CASES, INCLUDING THE SQUAMOUS-CELL CARCINOMA TYPES I, II, III, I-II, I-III, AND II-III

RADIATIONS	AVERAGE TIME BEFORE RECURRENCE OF CARCINOMA IN MONTHS				
	FIRST	SECOND	THIRD	FOURTH	FIFTH
One Reradiation	7.2				
Two Reradiations	11.7	23.0			
Three Reradiations	5.9	11.7	22.6		
Four Reradiations					
Five Reradiations	5.5	13.5	18.0	22	64

The results we have obtained in the various types of cell have been variable, and not always in accordance with the radioresistance of the cell. In a study of the epidermoid cancers we found that cell Group II (midripe) had an 8.5 per cent better average prognosis for all periods than the combined average for Groups I, II, and III, a 13 per cent

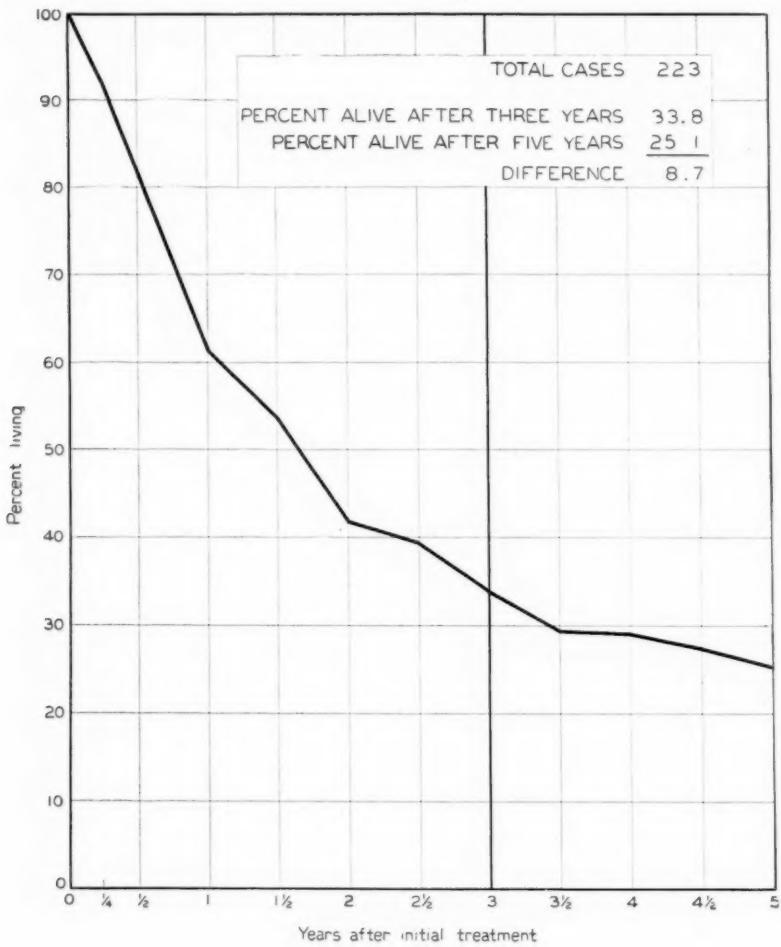


Fig. 2.

better prognosis than Group III (unripe), and an 8.7 per cent better prognosis than Group I (ripe), as shown in Fig. 1.

Adenocarcinoma of the cervix occurred in 20 out of 259 of our series, or a ratio of 1 to 12.95. This type of cell is generally classed as very radioresistant, and Regaud states that he has had very few cures in this type and advises operation. This is somewhat contrary to our experience, as in an analysis of a series of 147 cases with complete records, 13 were adenocarcinoma, with 4, or 30.7 per cent, of the patients living

five years. Of these 13 patients 9 received reradiations with a salvage of 4, and the 4 who were not reradiated did not survive.

Our experience confirms that of other observers that the three-year results are an index of the five-year cures. Fig. 2 shows that of 223 patients 33.8 per cent were alive after three years and 25.1 per cent after five years, the difference being 8.7 per cent. This difference is reduced if we take into account the normal mortality rate for two years at the average age of fifty that may be expected, so that we may judge with a fair degree of accuracy of the value of any line of treatment at the end of the three-year period.

It is apparent that in order to detect metastases in their incipiency, a frequent follow-up with a careful examination is essential. In no other way can we have the opportunity of destroying the recurrence while it is yet small and amenable to local treatment. It is useless to depend upon the subjective symptoms, as a recurrence in the vaginal tract will have gained considerable headway before giving rise to discharge, bleeding, or pain. The success of a follow-up clinic largely depends on the surgeon who operated upon the patient personally conducting the examinations. The patient will then come back as directed, but if the examination is left to an assistant, she will soon become delinquent. Furthermore, it is necessary for the surgeon who has studied and treated the original condition to watch the progress and changes that may occur, if a reliable appraisal of the condition of the disease is to be made. We grant that such a frequent personal follow-up is somewhat arduous, but we feel that we have learned much by this close observation of the course of the disease and that the results obtained have compensated us for our time and trouble.

It would not be possible for our cancer follow-up clinic to function satisfactorily if it were not for the valuable aid we receive from the Social Service Department, which cooperates with the Record Department, in tracing delinquent patients. The contact the Social Service makes with the patient while in the hospital is invaluable in educating the patient and her family to appreciate the importance of a strict attendance and the seriousness of neglect. We have been able to have a completed follow-up for five years of 96.4 per cent of our patients.

#### CONCLUSIONS

Reradiation in treatment of carcinoma of the cervix is of definite value in local metastasis.

Frequent examination at regular intervals should be made by the surgeon who applied the radium, to insure recognition of these recurrences sufficiently early for successful reradiation.

An analysis of 170 cases of epidermoid and adenocarcinoma of the cervix shows that nearly 50 per cent of the patients had more than one

radium treatment, and 26.5 per cent of the patients that were reradiated, lived five years or more.

Adenocarcinoma of the cervix was found in 13 of 147 patients studied. Nine of these 13 patients were reradiated and 4 of the 9 lived five years or longer. *The four patients that were not reradiated, did not survive five years.*

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## A FIVE TO FIFTEEN YEAR FOLLOW-UP STUDY OF ONE HUNDRED NINETY-TWO CERVICAL CANCERS\*

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(From the University of California Medical School)

**I**N 1926, I reported the five-year end-results in the treatment of 107 cancers of the uterine cervix. The study has been continued since then and another group of cases is now ready for review. Because the new series is also small, I am combining my entire material instead of presenting separate reports. This paper, therefore, is based on a study of 192 proved cancers of the uterine cervix treated between March, 1916, and March, 1926, in my series in the University of California Hospital. The five- to fifteen-year end-result is now known in all but 2 patients, each of whom escaped the follow-up after having been seen and examined for more than three years. At the time of the 1926 report, there were 3 cases lost from the follow-up. One of these has been found to be alive and well now ten years after treatment. The efficacy of the follow-up is further attested by the fact that no case has been lost from observation between March, 1921, and the present time.

**Material.**—The series is comprised of 159 patients who had had no treatment for their cancers prior to admission to my services and 33 women who had had operations for them elsewhere and had been referred to me later for radiation either as prophylaxis or for treatment of an evident recurrence. I have classified my material as follows: Group I, 17 cases; Group II, 26 cases; Group III, 74 cases; Group IV, 42 cases, and Group V, or Recurrent Group, 33 cases.

The grouping of cancer cannot be standardized because so much depends upon the individuality of the surgeon. The cancer of a certain patient may appear to one well-trained surgeon as a definite example of one group, whereas another equally competent man may assign it to an entirely different classification. For this reason there will always be disagreement concerning the proper grouping of any but the very early

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and very late cancers. A basic consideration makes a fair comparison of the result of treatment of any two series a most difficult or even impossible matter.

The proportion of the series that is comprised of Group IV cases assumes much importance when one comes to calculate the relative, or what are now termed absolute, cures in the series, since cures of Group IV cases are not likely. The percentage (26.6 per cent) of Group IV cases in my series is higher than that usually reported. Ward, in 1930, reports that only 4.4 per cent of his patients belonged in Group IV. On the contrary, the percentage of my cases in Groups I and II is high (27 per cent). The period of survival of Group IV cases should serve as an index as to the accuracy of the diagnosis in this group. The survival curve for my 42 patients of Group IV is shown in Fig. 1. Eight of the patients who were inoperable had a vesico- or rectovaginal fistula at the time of first treatment.

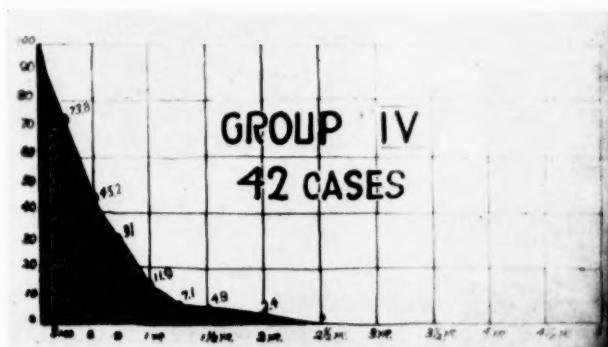


Fig. 1.—Survival curve of the forty-two cases of Group IV showing that three only survive more than one year.

**Treatment.**—Thirty-one of the patients in Groups I and II were operated upon by a modification of the Ries technic, most of them after preoperative radiation. Some of them also had postoperative radiation. Twelve patients in Groups I and II, comprising the bad surgical risks and the 2 patients who refused operation, were treated only with radium, or rarely also with deep roentgen-ray exposures. The other patients of the series were radiated only, except 3 patients who were inoperable but who were operated upon after the mass disappeared following radiation.

The age grouping is of interest in any cancer series. It has a practical bearing because few cures are expected in women of more than seventy years, since deaths from intercurrent disease during the period of observation at this time of life are far more common than five-year cures. Cancer in the young is also supposed to be more fatal than in women more mature, a point not proved by results in my series. The age grouping and five-year survivors are shown in Table I.

TABLE I. AGE GROUPING

AGES	TOTAL SERIES	FIVE-YEAR SURVIVORS
20-25	1	1
25-29	6	2
30-39	27	4
40-49	63	19
50-59	61	8
60-69	27	3
70-79	6	2
80-89	1	0
	192	39

**Family History.**—Textbooks usually state that comparatively few patients with cancer know of others in the family who also have had cancer. My experience is quite to the contrary. The more carefully the patient's history is taken, the more certain the student will be to obtain a positive family history of cancer. Especially is this true in patients who know something concerning two generations of their forebears. Table II shows the data obtained from the family history of my patients.

TABLE II. FAMILY HISTORY CARCINOMA

(Series January, 1916 to April, 1926)

Negative	138 (72.0%)
Positive	45 (23.3%)
Strongly suggestive	9 (4.7%)
Positive in 2 members	3
Positive in 3 members	1
Positive also in husband	1
Total	192

**Results of Treatment.**—The survival curve of the Groups I, II, III and IV cases should permit the visualization of my material. The mortality rate in the first year is due in large part to the deaths of Group IV patients. One year after treatment only 57.2 per cent of the entire series survive; two years after, 39 per cent remain. There is comparatively little mortality between the second and third years, but between the third and fourth years more than one-fourth of those who were alive at the end of three years succumbed to the disease. During the fourth year only approximately 10 per cent of those surviving at the end of the fourth year die from the cancer before the fifth year. More patients died during the first year than in the succeeding four years. The relative five-year cure is 20.8 per cent (Fig. 2).

**Group I and Group II Cases.**—These patients represent the group ordinarily considered operable from which must come most of the permanent cures of any series. Twenty-seven per cent (43 cases) of my entire series were classified as Group I and Group II cases. Twenty-five patients, or 58.1 per cent, of Group I and Group II cases remain as five-year cures.

The results varied, depending upon the type of treatment, and possibly also with the type of case. There were 31 patients in Groups I and II who had radical operations, with or without preoperative or postoperative radiation. There were 67.8 per cent five-year cures, without deduction for a patient lost after being well for three years, or for a patient who died of intercurrent disease, or for the four who died as a result of the operation.

TABLE III. GROUPS I AND II. RADICAL OPERATION WITH OR WITHOUT PREOPERATIVE OR POSTOPERATIVE RADIUM

Total number of patients	31
Lost, well at 3 years	1
Died of intercurrent disease	1
Died, result of operation	4
Died of cancer	4
Alive and well, 5 to 14½ yr.	20
Cancer death, 6 years	1
Five-year cures; no deductions	67.8%
Operative mortality	12.9%

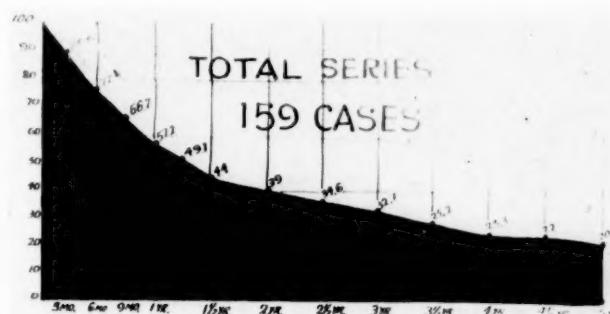


Fig. 2.—Survival curve for five-year study of 159 cervical cancers including all cases of Groups I, II, III and IV.

In contrast, there were 12 patients in Groups I and II who were treated only by radiation, with only 4 five-year survivors, or 25 per cent cure. The Group I patients who were not operated upon but were radiated only, consist of 3 patients, all with early growths, and all survive. One of the women, aged forty years, whose early growth has been cured for five and one-third years by 4,616 me. hours of radium, also developed a cancer of the nose requiring radium treatment, and one year later a malignant papilloma of the bladder. Another patient, a girl of twenty-two, had an early cancer which was not diagnosed until the pathologist found the tumor in tissues removed by a cervical repair. The patient refused further surgery and would not submit to radiation until forty-nine days after this tissue, 2 by 2½ by 1 cm., had been removed from the hypertrophied cervix. Whether the five-year cure resulted from the radiation or from the removal of a sluggish and early carcinoma might be difficult to determine.

TABLE IV. GROUP I. RADIATED, NOT OPERATED

Total number	3
Well, 5 years	3

One patient had a microscopic growth which was found after cervical resection. Radiated 49 days later. Does case belong in this grouping?

There were 9 Group II patients who were not operated upon but were radiated only. This group presents a rather sorry picture, since only 1 of the 9 survives as a five-year cure. The permanency of the only cure seems attested, since eleven years after treatment she seems to be cancer-free. Five of the others seemed cancer-free for three years, yet 4 of them died of cancer before four years had elapsed, and the fifth succumbed at four years, nine months after treatment. The sixth patient died two years after treatment from bowel obstruction of cancerous origin or possibly as a result of radium given when our experience was incomplete. Two others died from intercurrent disease when clinically free from cancer two and three years respectively after treatment. The five-year cure is but 25 per cent.

TABLE V. GROUP II. RADIATED, NOT OPERATED

Total number patients	9
Died within 3½ years	7
Died 4 years, 9 months	1
Died of cancer	6
Died of intercurrent disease	2
Alive, well 11 years	1

Operation refused, 2; contraindicated by heart disease, 2; by diabetes, 1; by poor general condition, 2; by age, 2.

Five-year Cures in Groups I and II, 25 %. No Deduction.

It might be argued that many of these cases were not fair tests for radium, since the entire group represented the bad risk patients who otherwise would have been treated surgically after preliminary radium. That cannot be disproved. Seven of the 12 women were over sixty years of age, 5 were over sixty-five, 1 being seventy-two and another eighty-two. The younger women had heart disease, diabetes, or refused operation.

Others, moreover, might not have grouped these cases as we did. Some of them might have belonged in Group III. I would have operated upon them, however, had conditions favored, since the operability of many of the patients that we did operate upon was at least as doubtful as those just cited above.

The 14 Group I patients who were treated by radical surgery all had early tumors. The largest was only 3 cm. in diameter. Four patients had very early growths, suspected rather than actually diagnosed as cancer before frozen sections were made. That very radical surgery can be safely performed on good risk patients with early tumor is shown

by the absence of surgical mortality or cancer deaths in this group; yet the series must be charged theoretically with 2 cancer deaths. One of these patients was lost after being well more than three years (her mail from us was not returned unclaimed from her postoffice address until more than five years after her first treatment), and one other patient

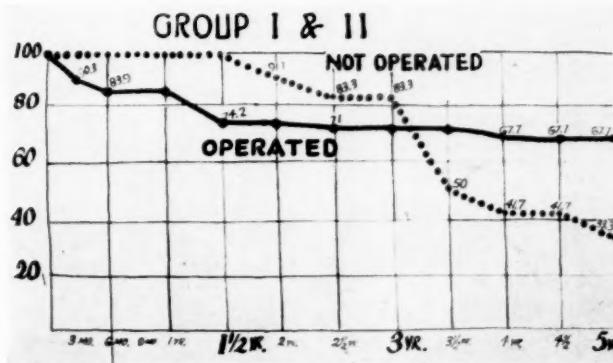


Fig. 3.—Contrasting survival curves of Group I and II cases that were operated upon with or without radiation with those that were not operated upon but were treated only with radium. Note the marked drop in the survival of the nonoperated but radiated patients who have remained well for three years and the comparative freedom from death of the operated cases that survived one and one half years after treatment.

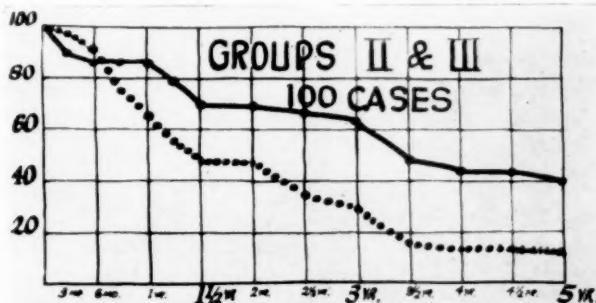


Fig. 4.—Shows survival curve of all Group II cases contrasted with those of Group III.

died of cerebral apoplexy one year after operation, at which time there was no sign of recurrence of cancer. These charges, necessary for proper statistics, reduce the cure to 85.5/7 per cent.

TABLE VI. GROUP I. RADICAL OPERATION ALONE OR WITH PREOPERATIVE OR POSTOPERATIVE RADIUM

Total cases	14
Lost, well 3 years	1
Dead from intercurrent disease	1
Dead from operation	0
Dead from cancer	0
Alive and well, 5 to 15 years	11
Dead from cancer, six years	1
Five-year Cures, 85.5/7%; No Deductions	
Operative Mortality, 0	

The 17 Group II patients that were operated upon and also radiated need no discussion. Nine of them remained as five-year cures. The mortality resulted early in the series and is attributable to the treatment of patients that really belonged in Group III. In order to check the accuracy of the grouping of II and III patients, we arranged a survival curve (Fig. 4). The differences between the groups is readily appreciable. The result of treatment is shown in Table VII.

TABLE VII. GROUP II. RADICAL OPERATION ALONE, OR WITH PREOPERATIVE OR POSTOPERATIVE TREATMENT

Total number patients	17
Lost	0
Dead from intercurrent disease	0
Dead from operation	4
Died of cancer	5
Died of cancer in 1 year	4
Died of cancer at 3 years	1
Alive and well, 5 to $1\frac{1}{3}$ years	8
Died of pneumonia, cancer-free at $5\frac{1}{2}$ years	1
Five-year Cures, 53%; Operative Mortality 23.5%	

Groups III and IV proved most disappointing, as we continued our follow-up of these patients for many years because so many of them who were cured for five years, later developed either recurrences or else other cancers.

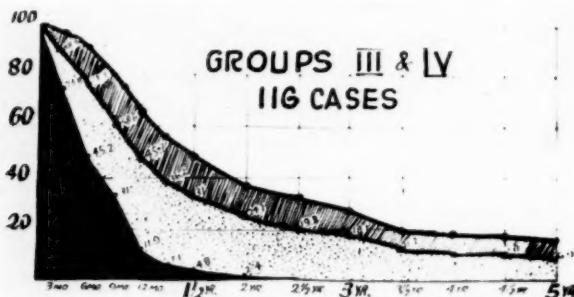


Fig. 5.—Survival curve of one hundred sixteen cases of Groups III and IV showing the hopelessness of the Group IV cases, and how their early demise affects the survival curve of the combined Group III and IV cases. Upper curve is survival curve of Group III cases, middle curve is for the combined Group III and IV cases, and lower curve indicates that for group IV cases.

There were 8 five-year cures (7.1 per cent) in this group, all of which have been followed subsequently. That patients apparently cured of cancer for years tend to die eventually of cancer seems attested by 2 patients who developed late recurrences: one died of intestinal obstruction nearly six years after her first treatment and the other has developed metastasis to the lower spine seven and a half years after radiation. This metastasis has grown very slowly and has not yet killed at the time of this report, more than two years after it first caused symptoms. During this time, the patient has been bedridden and cannot walk because the upper part of the sacrum has been eaten away from the lumbar spine.

Two other patients developed breast cancer, were operated upon and died from chest involvements five and a half and ten and a quarter years respectively after apparent cure of their pelvic cancer. The three who remain well have survived for five years, four months; five years, seven months; and ten years respectively. The known incidence of return of the original cancer after five years' apparent cure is 2 out of the 8 patients (25 per cent).

Properly included under this heading are 3 Group III patients who were operated upon after the tumor had disappeared following radiation. One of the 3 has survived twelve years. Her uterus, after removal, contained cancer cells which we regarded as dead or dying at the time but which at present we feel we know little about in view of the many late recurrences brought to our notice as the follow-up continues.

TABLE VIII. GROUPS III AND IV. CASES TREATED BY RADIUM ONLY, OR RARELY ALSO WITH DEEP ROENTGEN RAY

Total number of patients	113
Lost, well at $3\frac{1}{2}$ years	1
Died within 3 years	93
Died from 3 to 5 years	11
Five-year cures	8 (7.1%)
Died after five years, one each from	
intestinal obstruction	$5\frac{1}{2}$ yr.
Carcinoma lung (metastatic from breast)	$5\frac{1}{2}$ yr.
Carcinoma of breast	$10\frac{1}{4}$ yr.
Septic sore throat	$5\frac{1}{2}$ yr.
Living, well, $5\frac{1}{2}$ , 6 and 10 yr.	3
Living, metastasis to spine 10 yr.	1

TABLE IX. GROUP III. PATIENTS TREATED BY RADIUM AND THEN HYSTERECTOMY SEVERAL MONTHS LATER

Wertheim; died cancer	$1\frac{1}{2}$ years
Panhysterection; died cancer	$4\frac{1}{2}$ years
Incomplete Wertheim; living, well	$12$ years

*Recurrence After Nonradical Operations Elsewhere.*—Whatever the future will determine as to the relative values of truly radical surgery and of radium, there is no doubt whatever that the results of radium, even in inoperable cases, far surpass those of ordinary panhysterection even in cases deemed at least sufficiently operable to warrant its employment. The time has now arrived when the case has been proved that the ordinary panhysterection has no place whatever in the treatment of any but microscopic and, therefore, unrecognized cancers. If this paper which reports my results with radium and a very radical Wertheim type of operation would furnish the faintest reason for warranting others to undertake such a nonradical type of surgery as panhysterection I would feel that this entire study would be distinctly not worth while. A series of 26 patients treated by panhysterection performed by perfectly competent surgeons furnished no cure for more than four years in spite of my postoperative radiation treatment. Contrast

that with 7.1 per cent of cures in the inoperable cases that had never had other treatment than radiation. While there are some five-year survivors after incomplete operations, such as supravaginal hysterectomies or cervical resections, there is evidence forcing us to believe that these were radiosensitive but slow growing cancers that were not readily excited to growth by the trauma of the incomplete surgery.

TABLE X. RADIUM FOR PROPHYLAXIS OR RADIUM AFTER NONRADICAL OPERATION ELSEWHERE

	HYSERECTOMY PAN.	SUPRAVAG.	CERVICAL RESECTION
Number patients	26	4	3
Died cancer	26	2	1
Died 2 yr.	23	2	0
Dead between 2 and 3 yr.	1	0	1
Dead between 3 and 4 yr.	2	0	0
Alive and well 5 yr.	0	2	2

SUPRAVAGINALS

1 dead, cancer breast, in 8th year, well 6 years  
1 well 9 years, recurrence abd. wall, 6½ years

CERVICAL RESECTION

Both well 10 years, one had cancer of breast  
operated upon after 6 years, pelvic cure.

Tables XI and XII show the results of the follow-up when continued for more than five years. It is distressing to note that nearly one fourth

TABLE XI. CONDITION OF FIVE-YEAR SURVIVORS

<i>Dead</i>	
5 yr.	Recurrence breast cancer
5 yr. 4 mo.	Recurrence pelvic cancer
5 yr. 5 mo.	Intestinal obstruction—recurrence?
5 yr. 6 mo.	Septic throat; no recurrence cancer
5 yr. 8 mo.	Pneumonia; cancer-free
8 yr.	Cancer breast
10 yr. 3 mo.	Cancer breast
<i>Living, with cancer</i>	
7 yr. 5 mo.	Pelvic recurrence (6½ yr.)
8 yr. 10 mo.	Pelvic recurrence
9 yr. 10 mo.	Operated 6¼ years for breast cancer Now no signs of recurrence
10 yr.	Lumbar vertebrae and sacrum separated by metastases
<i>Living, with advanced pulmonary tuberculosis</i>	14 yr., 4 mo.
<i>Well, apparently cancer-free</i>	
5-6 yr.	8
7-8 yr.	3
8-9 yr.	6
9-10 yr.	1
10-11 yr.	2
11-12 yr.	2
12-13 yr.	2
13-14 yr.	2

of the five-year survivors died subsequently from recurrence of their original cancer or developed other cancers of equal importance.

In conclusion, we present our results for all groups.

TABLE XII. FIVE-YEAR CURES

GROUP I	14 patients operated upon and radiated 3 patients radiated	12 patients, or 85.7%, cure 3 patients, or 100.0%, cure
GROUP II	17 patients operated upon and radiated 9 patients radiated	9 patients, or 53.0%, cure 1 patient, or 11.0%, cure
GROUP III	71 patients radiated 3 patients radiated and operated upon	8 patients, or 11.3%, cure 1 patient, or 33.0%, cure
GROUP IV	42 patients radiated	0 patient, or 0%, cure
GROUP V	43 patients radiated	4 patients, or 12.1%, cure
Total	192 patients	38 19.3% cure

CONCLUSIONS FROM A STUDY OF FIVE-YEAR CURES IN A  
SERIES OF 121 CASES OF CARCINOMA OF THE  
CERVIX UTERI\*

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OUR experience at the Barnes Hospital of the Washington University Medical School in the treatment of carcinoma of the cervix with radium and x-ray, now extends over a period of ten years. Preceding that time surgery was the only established resource of the profession in cancer of the cervix. While the splendid development of surgery in the form of the radical operation for this condition registered a brilliant triumph and rescued many patients from death by cancer, the operation itself carried a high mortality. The persistent world-wide search for a less dangerous remedy brought out many so-called "cures." Time and time again the profession was carried to the pinnacles of hope, only to be dropped to bitter disappointment. The repetitions of this process naturally made gynecologists very critical of new remedies for cancer. Radiation, like other proposed remedies, had to meet this healthy spirit of skepticism and analysis, which constitutes the cancer patient's only protection against fake "cures" and mistaken "cures." In the beginning of radium work and x-ray work, the results justified continued skepticism. However, improvements in materials, technic, and increasing experience in the use of these powerful remedies, finally produced results that stand up under the most rigid analysis, and that placed radiation alongside surgery as an effective remedy for cancer of the cervix.

\*Read at the Fifty-sixth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 18-20, 1931.

Experimentation is going on at an increasing rate in many well-equipped institutions, and we hope the future will bring a still more effective remedy. But for the present the only reasonable chance of cure rests on these two remedies, effective surgery or effective radiation.

Effective radiation treatment began a decade ago. Much experimentation in radium and x-ray work was carried on before that time, but it was about that time that radiation reached the effectiveness that established it as a real cure for carcinoma of the cervix. Radiation cured many cases that were beyond reach by even the most radical operation. Its striking effect in such cases caused it to be used earlier and earlier in the disease, with increasingly good results, until now it has supplanted operation in all except the very earliest cases. Even in these very early cases, radiation results are challenging those of surgery.

The change in treatment brought about by the work of ten short years is very striking, even startling. The physicians now coming on the stage of action can hardly appreciate the cancer treatment situation only a decade ago, and physicians who have not kept up with these revolutionary cancer developments are in no position to advise a patient with cancer of the cervix.

As part of our study of the various questions connected with cancer of the uterus, we have just completed an analysis of the series of cases treated more than five years ago. This series comprises the patients handled in the teaching wards of the Barnes Hospital, and also my private patients and those of Dr. Q. U. Newell, associate in the teaching.

The laborious statistical analysis was carried out by Dr. Newell. Only those who have been in close touch with such work, can realize the many difficulties to be overcome in various directions. For example, the tracing of the "disappeared" cases to final outcome, required innumerable visits by the social workers of the Service, and letters to patients and their physicians and neighbors (as to where individuals had moved), and to postmasters and to bureaus of vital statistics, and finally to the Red Cross workers in various towns, who gave much help in certain instances. The pathologic grouping by cell-types was carried out by Dr. Robt. J. Crossen, who reviewed all slides, and in many cases cut new sections for study.

This series showing five-year results, consists of 121 cases, treated from July 1, 1921 to April 1, 1926. Of these 121 carcinomas of the cervix, 108 were squamous-cell carcinoma and 13 were adenocarcinoma. Classed clinically according to extent of involvement, 2 were in Group I (cervix only involved), 1 was in Group II (slight parametrial involvement but no fixation of uterus), 108 were in Group III (extensive parametrial involvement with fixation of uterus), and 10 were in Group IV (extensive involvement of vagina or bladder or rectum as well as of parametrium). Fifteen patients could not be traced, in spite of all the various expedients employed. These lost patients were counted as dead from cancer, though some of them may be living.

The 2 patients in Group I were subjected to operation without radiation. They are both living, one nine years and the other eight years after treatment. One of these patients developed a ureterovaginal fistula eight days after the radial abdominal operation. Six months later (February, 1922) the right ureter was transplanted into the bladder. Recent follow-up showed no urine from the right ureter. The right kidney has apparently atrophied to complete nonfunction, but the patient is in good general health without local symptoms. The one patient in clinical Group II was given 3800 mg. hr. of radium and, after seven days, abdominal hysterectomy was performed. This was followed by deep x-ray therapy two weeks after operation and again in three months. This patient is living, seven years after treatment. Of the 108 patients in clinical Group III (extensive involvement of parametrium with fixation of uterus to pelvic wall), there were 24 five-year survivors and 21 of these are still living, some as long as eight years since treatment. Of the 10 patients in clinical Group IV (extensive involvement of vagina or bladder or rectum in addition to parametrium), not one survived five years.

The 100 per cent survival of patients in clinical Groups I and II is, of course, of no special statistical significance. These 3 patients happened to survive, but a glance over later series shows a survival percentage more nearly approaching those in recent literature for like involvement and similar treatment. The very large proportion of advanced cases in this series, makes the percentage of cures decidedly less than if there had been a fair proportion of early cases. However, of the 108 patients in clinical Group III (parametrial involvement fixing uterus to pelvic wall) 21 per cent were cured, a gratifying percentage for such advanced cases.

The conclusions presented in this paper, as to choice of treatment in different classes of cases, are of course based on cases treated in the last five years as well as on those treated more than five years ago. Each case is studied and treatment decided on, in the light of the experience gained in preceding cases. The difficulties encountered in securing results with the different methods of treatment in the different classes of cases—lessons from the failures and from the successes of the last ten years' work with this disease—all enter into the conclusions given later.

In every case admitted to the series, the diagnosis of carcinoma was confirmed by microscopic examination. Classifying the 108 squamous-cell carcinomas according to cell type, 23 were Type I (preponderance of mature cells), 48 were Type II (transitional), 11 were Type III (preponderance of immature cells, embryonal type), and 26 were indeterminate.

The "indeterminate" were indeterminate, usually, because of partial necrosis of the cells, the cell picture being sufficiently clear to show carcinoma but not sufficiently clear to establish the predominating cell

type. This emphasized the importance of certain details in specimen excision. The older, probably necrobiotic tissue, should be avoided and the specimen should reach into the active penetrating portion of the growth. On the other hand, it is important in specimen excision to avoid penetrating beyond the protective leucocytic wall, which guards against the lymphatic spread of the virulent bacteria often present in the cervices of a carcinomatous mass. Another reason for care in specimen excision is that a very small specimen may not go deeply enough to reach the carcinomatous process, taking in only the inflammatory and circulatory disturbance overlying it. In some cases of clinically appearing carcinoma of the cervix, the specimen removed at the radium treatment showed only chronic cervicitis. In certain of these cases I am satisfied from personal observation or subsequent development that there was a carcinoma, but as they lacked microscopic confirmation, they were excluded from the series, and the number of cured cases was reduced accordingly.

Classifying the 24 radium five-year survivals according to cell type, there were 5 survivals of the 23 showing cells of Type I (mature cells), 8 survivals of the 48 having cells of Type II (transitional), 5 survivals of the 11 showing cells of Type III (embryonal), and there were 6 survivals of the 26 of indeterminate cell type. Of the two very early cases subjected to operation only, and still surviving nine and eight years afterward, both were squamous-cell carcinomas—one showing cells of Type I and the other indeterminate. The one case in clinical Group II (some parametrial involvement, but no fixation of uterus), subjected to radium and operation and subsequent x-ray and still living after seven years, was adenocarcinoma of the cervix. The cell type apparently does not have a great influence on survival of the patient, certainly very little compared to the clinical classification according to extent of growth. Referring to the preceding clinical classification based on extent of growth, there were 100 per cent survivals in clinical Groups I and II, 21 per cent survivals in clinical Group III, and not a single survival among the patients in clinical Group IV. However, the survival of 5 out of 11 having cells of Type III compared to survival of 5 out of 23 having cells of Type I, furnishes further confirmation of the generally-held opinion that radiation is decidedly most effective in the immature or embryonal cell type. The other conditions were practically the same for the different cell types, all except 3 of the 27 survivals being in clinical Group III (extensive parametrial involvement with fixation of uterus) and receiving radiation treatment only.

I shall not trouble you with an array of statistical tables. In the various clinical classes and pathologic types our results do not differ materially from those that have been recently presented in the literature. The subject of carcinoma of the cervix is such a complicated one and presents so many clinical and pathologic variations and special problems in the adaptation of the details of treatment to the individual

case that it overflows tabular analysis. As we treat and observe patients day by day, endeavoring to give each patient the benefit of experience gained in preceding cases, our conclusions and practice are influenced by many things that cannot be presented in statistical form. Consequently, in helpfulness toward effective treatment, a very important feature of a series-report is the summary which presents the observer's experienced conclusions on various points in question. There are three disputed phases of this subject on which I have reached very definite conclusions, (1) as to treatment for very early cases, (2) as to the essentials of effective radium treatment, and (3) as to prophylaxis of cancer of the cervix.

Thousands of workers in this field look to the members of the Society for guidance on these serious questions. I hope the discussion will bring out such general expression of experienced conclusions, as to give material help to those who are seeking light, and thus improve the treatment and results for their patients. Many patients are being subjected to operation who could be given a much better chance for life by effective radiation. Also, many patients are being treated with radium in a manner that falls far short of the effectiveness to which they are entitled. Hence the importance of clear and definite statements of conclusions by those who have had a large experience in the treatment of such cases.

#### 1. WHAT IS THE BEST TREATMENT FOR THE VERY EARLY CASE?

The treatment of cancer carries a greater responsibility than the treatment of ordinary diseases. It has been said that a considerable proportion of human ailments are self-curerative if given time, but cancer does not belong to that class. In cancer of the cervix, only the judgment and skill of the physician stand between that patient and certain death within a very limited time. The patient's survival is determined largely by the physician's judgment in the choice of remedy and his thoroughness in its application. Consequently, it is with a profound sense of responsibility that the physician makes the selection of remedy for the individual patient.

In the very early carcinoma of the cervix, is it surgery or radiation or a combination of the two, that will give the patient the best chance to survive?

Theoretically, we should be able to cure these patients with radium, with as great certainty and with far less danger than with the knife. But so far the actual results do not seem to justify entire displacement of the knife by radium in these early cases. It is hoped that advance in the technic of radiation will eventually place it far ahead of operation in the percentage of cures even in the early cases, but so far it has not been demonstrated that this hoped-for result can be secured uniformly.

The crux of the situation is that there is still uncertainty as to how far radium will be effective in the individual case. It gives wonderful results in most cases, but, on the other hand, in some cases it stops short of expected effectiveness. And the disconcerting thing about it is that we do not know why it fails where apparently it should succeed. Outside of the technical details of its application, its effect is evidently modified by the type of cancer cell present, by the type of tissue cell in the area, by the condition of the tissue cells in the particular case, and by the resistance or defensive power, both local and general, of that individual. These important items vary with each patient and we know so little about them, even in the normal or typical individual, that it is not strange there should be certain unexplained variations in results in clinical radium work.

It is this uncertainty that makes entire dependence on radiation hazardous in these very early cases, in which, presumably, no cancer cell has yet penetrated beyond the uterine border. We know what can be done with the knife. The uterus can be removed with fair safety and thus the contained cancer cells completely eliminated. We do not know the extent of effectiveness of radiation in an individual case until it is tried in that case. And in the time required for trial by radiation, the chance of cure by operation slips away.

On the other hand, entire dependence on operation in these cases carries the serious hazard of leaving cancer cells beyond the operative area. No matter how early the cancer, some cells may already have been carried far out in the parametrium. Radiation gives the chance of devitalizing such outlying cancer cells. Consequently, the patient is given the best chance of cure in these early cases by the employment of both operation and radiation—operation to insure certain removal of all cancer cells in the uterine wall, and radiation to devitalize any outlying cancer cells that may be present.

Operation is carried out in the very early cases only on the supposition that no cancer cells have penetrated beyond the uterine border, and that a comparatively safe hysterectomy gives a good chance of complete eradication of all cancer. Consequently, such operation should be a hysterectomy with the removal of only as much parametrium and adjacent vaginal wall as can be excised without material increase in the risk.

Having decided to give the patient with a very early carcinoma the benefit of both operation and radiation, then arise certain questions of detail. Should the radiation be in the form of radium or x-rays? When conditions are favorable for the application of radium, it is the most effective form of radiation for the devitalization of cancer cells within a short distance, such as in the cervix and parametrium. The function of the more widespread x-rays is to devitalize cancer cells that lie beyond the reach of the concentrated radium dose in the center. Consequently, from the radiation standpoint, it is advisable to give a concentrated

radium dose in the cervix before operation and follow this after operation with deep x-ray therapy embracing the whole pelvis.

From the surgical standpoint, however, the effect of a radium application in increasing the danger of subsequent operation must be considered. In my experience, radium application to the cervix tends to increase materially the danger of an abdominal hysterectomy carried out within a short time thereafter. This has been so evident and marked that I have ceased to use preliminary radium treatment in those cases in which the hysterectomy must be abdominal, depending on the x-rays instead. In the cases that can be handled by vaginal hysterectomy, I give a heavy dose of radium, as though depending on that for the cure, and then do the vaginal hysterectomy with removal of adjacent parametrium and vaginal wall. The vaginal hysterectomy is carried out very soon after the radium treatment, preferably at the same sitting at which the radium is removed, in order to minimize the inflammatory reaction and bacterial invasion which increase daily for several days after any such extensive disturbance about the cervix. I formerly waited several days after removal of the radium, but became convinced that this wait increased the danger of serious infection at operation. Some have proposed to delay the operation for some weeks, until the inflammatory reaction has subsided, but there are two objections to that plan. By that time the leucocytic infiltration has increased the difficulties of operation and, still more important, precious time has been lost—time enough for the condition to change from a strictly cervical limitation of the cancer to that in which the cancer has extended beyond.

Another question concerns the time for the x-ray treatment. In the early cases subjected to abdominal operation, should the supplementary x-ray treatment be given before or after operation? It seems to me much safer to do the operation immediately and reserve the x-ray treatment for later, when the patient has sufficiently recovered from the operation. In these very early cases the main object, to which everything else should yield, is the removal of the uterus before any cancer cells extend beyond its border. No one can tell what day the malignant cells will metastasize. Every day of waiting carries that danger. Consequently, there should be no delay, except that necessary to prepare the patient properly for the serious operation. Again, x-ray treatment given shortly before operation would increase the danger of the operation. X-ray treatment of sufficient depth and extent to devitalize cancer cells in the pelvis, has a marked upsetting influence on digestion and metabolism. Having to be given through large masses of tissues, including the intestines, the general effect is quite different from a radium treatment in which the dose is practically limited to the affected area. One of the reasons that an abdominal operation always carries a certain amount of risk, is that we cannot be certain of the margin of reserve in the patient's vital functions. Consequently, we should avoid any preoperative measure which materially disturbs the metabolism. In

these early cases prompt careful operation before the malignant cells pass beyond the border of the uterus is the vital thing, the x-ray treatment, on the supposition that some cells may already have metastasized, being of secondary importance.

The above plan of treatment for the very early case is based on the assumption that the patient is a good operative risk. If the patient is a poor operative risk, then her best chance of survival cancer-free, may be through radiation without operation. Another factor that may influence the decision in a borderline case, is the "malignancy index" according to cell type. Radiation has most effect in tumors with a preponderance of immature cells (Type III). This embryonal type is also most rapid in growth and in metastasizing, and consequently is less favorable for operation. On the other hand, the tumors with a preponderance of mature cells (Type I) are less influenced by radiation. This adult type is also slow in growth and in metastasizing, and hence is more favorable for operation. However, one difficulty in using the cell type as a guide in treatment is that the small specimen removed for diagnosis may not show the predominating cell type of that tumor.

The decision for or against operation, and of the extent of operation, turns on a balancing of the hazards pro and con: the hazard of operation, the chance of failure of radium to kill the cancer cells in that individual, and the chance of metastasis near and far. On account of the latter danger, it is advisable to employ deep x-ray therapy to supplement other treatment, whether the other treatment be radium or operation.

## 2. WHAT ARE THE IMPORTANT ITEMS IN EFFECTIVE RADIUM TREATMENT OF CANCER OF THE CERVIX?

This powerful remedy requires experienced judgment and skill in its use. It is as potent as the knife and in inexperienced hands may produce as disastrous results, either in the form of injury to adjacent organs or as failure to obtain results that might have been obtained by a really efficient application.

The beneficial effect of radium depends on the careful carrying out of many details. Only by careful study and accurate execution of numerous details, can the patient be given the best chance of cure. The essential details may be conveniently grouped under the following four headings: (a) careful study of conditions present in the individual case, (b) maximum dose of radium at first application, (c) supplementary x-ray treatment, and (d) follow-up and treatment of recurrences.

a. *Careful Study of the Special Conditions Present in Each Case.*—This is necessary in order to give the most effective radiation in the individual.

The patient's chance for life lies in devitalization of the outlying cancer cells. It is in this particular that radium can go further than the

knife or the cautery, killing cancer in inaccessible situations beyond the reach of these other measures. One must not allow his attention to be diverted from this vital point by the striking effect of radium on the nearer portions of the cancer. The destruction of the large mass of cells in the sloughing area and consequent healing are only incidental to reaching cancer cells much further out. This local destruction could be accomplished with the knife or with the cautery; there is nothing distinctive about it. The distinctive and superior effect of radium is the extension of differential killing effect to include cancer cells at the outermost margin of the growth. If we do not reach these outlying cells, our radium treatment has failed, except as a temporary palliative measure.

The size of dose of deeply penetrating rays that can be given depends on a number of factors, including the location and size of the cancerous mass, the amount of involvement of each of the various organs in the immediate vicinity, the extent and direction of ulceration, and especially the fixation of the bladder and rectum in relation to the carcinomatous infiltration. The accurate determination of these conditions and the utilization of that knowledge in effective radium treatment require a large amount of experience and skill in gynecologic work. While in some situations the radiologist without special local knowledge may give effective radium treatments, in carcinoma of the cervix conditions are such that the most effective treatment can be given only by the skilled gynecologist with adequate radium training. His special knowledge of pelvic anatomy and pathology and his training in accurate pelvic palpation and diagnosis must all be utilized in the supreme effort to reach the marginal cancer cells with effective radiation.

b. *Give the Maximum Dose at the First Application.*—The danger of recurrence lies in the deep cancer cells. Our real problem, as just stated, is to reach and devitalize these deep-lying cells. The best chance of doing this is by giving as large a dose as practicable of the deeply penetrating rays at the first application. This is accomplished by placing the heavily screened radium in the center of the cancerous infiltration and then packing away the rectum and bladder as far as possible, so as to allow the maximum dose. Never again will the conditions be as favorable for a devitalizing dose to the outlying cells as they are at the first application. If the opportunity is missed then, it will not return. I reached this conclusion near the beginning of my radium work a decade ago, and in all that has transpired since I have seen no reason to change it. On this point this series shows that of 17 patients receiving 5000 mg. hr. at the first application, 6 were cured (35 per cent), while of 79 patients receiving smaller doses, 14 were cured (18 per cent). All of these patients were in clinical Group III; i.e., there was parametrial infiltration fixing the uterus.

c. *Supplementary Deep X-ray Therapy.*—A heavy dose of radium in the center of the cancerous infiltration is undoubtedly the most effec-

tive form of radiation for devitalizing cancer cells within a reasonable distance. But in any case there may be scattered cancer cells beyond the reach of the radium. Deep x-ray therapy may devitalize these cells, which otherwise would not be reached.

While x-ray therapy is not so reliable as radium in its devitalizing effect, it is effective in some cases. I recall a striking case in point.

The patient, aged forty-eight years, who was a physician from a distant state, came to me in 1922 with a widespread carcinomatous process in the pelvis including extensive involvement of the parametrium and the vaginal and rectal walls. The infiltration had extended to the sphincter, with loss of fecal control. In spite of her suffering and the apparent hopelessness of the condition, the patient faced the situation with a calmness and interested cooperation which were inspiring. As conditions were not favorable for radium, x-rays alone were used. There seemed to be some checking of the process, and this encouraged continuation of the x-ray treatment, which was pushed to the limit by our roentgenologist, Dr. Sherwood Moore. In the course of several months, the ulceration healed, the dense infiltration diminished, fecal control largely returned, and the suffering disappeared. After two years, the patient was able to resume her practice to some extent. Examination at that time showed much scar tissue in the pelvis, fixing the structures to the pelvic wall and extending down the rectovaginal septum, but it was much softer than the former dense nodular infiltration, and showed no evidence of malignant activity. The marked improvement continued, the patient coming occasionally for observation and examination.

In March, 1928 the patient contracted pneumonia, of which she died. In the absence of complete autopsy, some deep recurrence cannot be excluded, consequently the case cannot be classed as a cure. However, the patient was rescued from severe suffering and lived in comparative comfort for six years after x-ray treatment alone of an apparently hopeless condition.

*d. Careful Follow-Up of Cases and Treatment of Any Local Spots of Recurrence.*—The importance of this and the good results often attained have been emphasized by a number of writers, and especially by Ward in his excellent presentation of the work of the Woman's Hospital of New York.

The local recurrences that are likely to yield to small radium applications are those in the vaginal wall, due to cancer cells that have wandered down beyond the reach of the radium applied in the cervix. If such a spot is recognized early, before any deep penetration, it may be cured by the dose of radium permissible in these conditions, especially by the employment of emanation in the form of gold or platinum "seeds." Of course, a large dose of radium, such as given at first, is not permissible after the bladder and rectum have been drawn in and fixed by the postradium sloughing and scar formation, for it would quickly penetrate into one or both of these organs.

Where there is deep recurrence, x-ray therapy is the main reliance in checking it. Various efforts have been made to reach these deep recurrences with an effective dose of radium, principally through an abdominal incision. Some good results have been reported but, on the whole, the outlook in this direction is not encouraging. The difficulty

is that a deep recurrence that can be recognized is usually a widespread recurrence, requiring such a large dose of radium that it can hardly be safely applied in the midst of large blood vessels and hollow organs. The best hope for these cases probably lies in the super x-rays, running up to 600,000 volts, which are now being developed.

The above four items in radium treatment of cancer of the cervix are the most important in endeavoring to give the patient the best chance to survive. There are two other items of considerable importance, though they are concerned not so much with devitalization of cancer cells as with the patient's general health. I refer, first, to measures for minimizing the spread of infection and, second, to efforts to build up the patient's health and general resistance.

Bacterial invasion is a serious accompaniment of carcinoma of the cervix. Bacteria swarm in the cancerous ulcerations and papillary formations and penetrate the tissues underneath, and complete disinfection is practically impossible. Any extensive manipulation in the area is likely to stir up additional bacterial activity. Pyometra is one form of such disturbing inflammation. A carcinoma of the cervix tends to occlude the cervical canal, blocking drainage and causing a collection of pus in the uterine cavity. This is one of the causes of fever and pelvic pain and tenderness of the corpus uteri in certain cases of cancer of the cervix. The diagnosis is confirmed by a flow of pus when a uterine forceps is introduced into the cavity and opened. Even when there has been no pyometra before, it may develop after radium treatment from the swelling of tissues about the cervical canal. To overcome pyometra, or prevent its occurrence, I have for several years made a practice of putting a small rubber-tube drain in the uterine cavity along with the radium, and leaving the tube in for a week or two afterward.

The other and more serious form of infection is that in which the bacterial invasion extends past the protective leucocytic wall about the carcinoma, and produces general sepsis. To prevent this, it is important to avoid making deep incisions or introducing needles that extend beyond the leucocytic wall of protection. This is one of the objections to the use of needles, the efficacy also of which in this situation I have always doubted. Several years ago, when this method of using radium was very popular, I visited a gynecologist who was using it, in order to see just how the danger of infection and of injury to ureters and blood vessels was avoided. In treating a patient, after disinfection of the surfaces the radium needles were inserted with critical care to avoid important structures, and everything seemed just right. In four days the patient was dead of sepsis, which began promptly after the needle treatment. The carcinoma was of only moderate extent and the patient in fair general condition, just such a case as ordinarily responds splendidly to radium applied within the defensive leucocyte wall.

The patient's general health and resistance are of course important in the fight to overcome invading cancer, and the patient should be

toned up by all available means, including blood transfusion, when her condition requires it. The helpfulness of transfusion in cases with low hemoglobin has been especially emphasized by Ward, in his article already referred to.

In connection with maintaining the patient's resistance, the depressing effect of general anesthesia is to be considered. General anesthesia is to be avoided when practicable. Nearly all of our radium applications were made simply under hyoscine-morphine sleep. Only in exceptional conditions did we find it necessary to supplement this with short gas or ether inhalation.

### 3. PROPHYLAXIS OF CANCER OF CERVIX

This is practicable and presents the best hope of further material reduction in deaths from carcinoma of the cervix. The time to cure cancer with greatest certainty is before it starts. Cancer of the cervix comes from long-continued irritation in the form of chronic cervicitis, usually accompanied with laceration, infiltration, and cystic change. These lesions are very obvious, and their rôle in cancer origin is generally known, and yet they are allowed to go on and on well into the cancer age. Great pains are taken, in cases of chronic cervicitis, to detect the first signs of cancer, so that treatment for cancer may be promptly instituted; whereas a safer plan is to remove the chronic cervicitis promptly, before it becomes cancer.

Chronic cervicitis may be cured by simple conical excision of the affected area of the cervix, and thus cancer is prevented. But when the process has once advanced from inflammatory hyperplasia to cancerous proliferation, cure is uncertain by even the most radical methods. Why delay and procrastinate, until the possibility of cure by a simple operation has slipped away?

I believe that this is a very important phase of the cancer problem. Repeated insistence, by gynecologists in their writings and in their teaching to students, that it is imperative to make prompt removal of chronic irritation in the cervix in the latter part of the childbearing period, will greatly aid in establishing this practice. When this practice becomes general throughout the profession, it will save many patients from death by cancer.

UNIVERSITY CLUB BUILDING.

## BASAL METABOLIC RATES IN LATE PREGNANCY AND THE PUEPERIUM\*

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FROM various reports in the literature concerning changes in the metabolic rate during pregnancy, one must conclude that there is undoubtedly an average increase of 15 per cent in the woman who is at full term, as compared to her rate in the nonpregnant state. Various authors have indicated that this increase in their determinations is around 5 per cent, whereas others have reported an increase of as much as 30 per cent for the normal pregnant woman.

According to DuBois, who reviews the subject of basal metabolism in pregnancy in the latest edition of his monograph on basal metabolism, during the first half of pregnancy the weight production of conception is negligible in comparison with that of the mother. Later there is a more rapid development of the fetus and also of the placenta and the inert liquor amnion. He mentions that matters are still further complicated by changes in body weight and by a pressure upward on the diaphragm which increases the labor of respiration. He states also that after parturition there are the new factors of involution of the uterus and development of the lacteal glands. Considering the above mentioned factors, he thinks it is difficult to interpret the rather limited work on this subject.

In a very thorough study on a single case throughout pregnancy and the puerperium, Sandiford and Wheeler found an increase in metabolic rate from the beginning of pregnancy with a rate of minus 3 per cent to a rate of plus 8 per cent. The day after delivery the rate had dropped to minus 6 per cent and remained in this neighborhood during the first week of the puerperium. By applying the Lissauer formula and estimating from this the surface area of the fetus, they concluded from the calculation of this case as well as from other cases in the literature that the energy production of a unit mass of the mother's protoplasmic tissue remains unchanged throughout the course of pregnancy, and that such increases in the total heat production as occur are due to the increasing mass of active protoplasmic tissue, consisting in large part of fetal tissue and in lesser part of maternal structures. The placenta was not considered in these calculations. The fetus, because of its uterine environment, should show an energy production much less comparatively than that of the mother or of the newly

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born. During pregnancy a hypertrophy of the thyroid probably exists. Considering these things, it would seem that Sandiford's estimations are unusually interesting.

This work has interested us because numerous observations have been made during pregnancy which would indicate that there actually exists an increased activity of the thyroid gland normally. Changes in the thyroid gland are well known to occur in pregnancy, hypertrophy of the gland being definitely observed in from 70 to 80 per cent of all cases, according to Seitz. Changes in the gland are chiefly the increased vascularization, and the increase of the epithelial elements with a storage of colloid toward the end of pregnancy. These changes are strikingly shown by Seitz in the rabbit.

One of us, for his own satisfaction, studied a series of pregnant guinea pigs. It was observed that during the early half of gestation there was a marked increase of the epithelial elements with storage of colloid during the latter half of pregnancy, this storage disappearing to some extent during the three or four days before labor sets in.

Davis was able to show that if a woman with a normal thyroid had sufficient iodine during the course of normal pregnancy, her basal metabolic rate will remain within the normal limits, although it may show a slight increase toward the end of pregnancy. Further, Marsh and Murlin, who studied premature and undersized infants, confirming Talbot's work, found that premature infants produced 26.25 calories per square meter per hour, which is considerably less than for a middle-aged or young adult. Benedict and Talbot found for the newborn an average of 27.7 calories per square meter per hour. This should indicate that the protoplasmic tissue of the fetus in utero on account of its environment should be even less than that of the premature or newly born infant.

Recent investigations have shown rather clearly that the anterior pituitary has a definite influence on the activity of the thyroid. Bugbee and his associates, in discussing the function of the anterior portion of the pituitary, mention the recent work of Foster and Smith, which showed that the removal of the whole pituitary gland caused a 35 per cent reduction of the metabolic rate. This could be restored by daily transplantation of anterior pituitary gland, transplantation of posterior pituitary being without effect. This work with that of other investigators, such as Schwartzbach and Uhlenhuth, and Crew and Wiesner, leads to the belief that one of the hormones of the anterior pituitary activates the thyroid gland. This is interesting in view of the hypertrophy of the anterior portion of the pituitary gland in pregnancy, and also the overproduction of certain of its hormones.

In very recent observations Bockelman and Scheringer, determining the iodine content of the blood through pregnancy, found a distinct rise in blood iodine from the second until the tenth lunar month, their figures being 15.5 gamma per cent in the second month to 22.5 gamma per cent during the tenth month and showing a definite drop during the first two weeks of the puerperium. This confirms the previous work of Maurer, who also observed the rise in blood iodine toward the end of pregnancy.

Also recently, Anselmino and Hoffmann, by determining the action of serum of nonpregnant and pregnant women on the excised livers of mice, show that there is a glycogen-diminishing substance in the blood which is demonstrated more markedly in the serum of the pregnant woman. They concluded from this work that there is present in the blood of a pregnant woman a substance which causes a more marked diminution of the glycogen of the mouse liver. This can be demonstrated from the second month of pregnancy and increases toward the end of pregnancy, but diminishes almost completely by the eighth day postpartum. They consider this due to an increase of thyroid hormone in the blood.

As the thyroid gland is known to exhibit hypertrophic changes during pregnancy, one could assume that the basal metabolic rate should actually be increased in the mother. The deductions of Sandiford and Wheeler are contrary to this, and it is this that suggested the present study. Much of the data just mentioned have been accumulating since our work was started and it seems that this is further evidence that there is actually an increase of thyroid activity during normal pregnancy.

In view of these facts, we believed that the study of cases where consecutive determinations have been made daily before delivery and in the puerperium should throw some light upon this subject. During the last two weeks of pregnancy interesting changes are noticeable in the mother, chief of which is the fact that her weight does not usually increase in the same degree as previously, often it is stationary, and during the last week, sometimes actually decreases, although the uterine structures are continually increasing until term. This latter fact is well known clinically, because women who become definitely overdue frequently have unusually large babies. It was suggested, therefore, that metabolic rates determined in this manner daily for two weeks before and at least one week after delivery, might show some interesting changes. We have begun such work and this study is presented in the nature of a preliminary report, 17 patients in all having been observed.

The patients were hospitalized from two to three weeks before delivery and were put to bed at night after dinner and were not allowed to get up until after the determinations had been made. All other standards concerning these determinations were fully carried out. The calorimeters which were used were of the Krogh-Hagedorn and Benedict-Roth types. They were checked against the Benedict-Roth apparatus in the Department of Medicine. This is mentioned because the rates in several instances are considerably lower than are usually given for normal pregnant women, but since it is generally considered that figures formerly given were too high by about 8 per cent (DuBois), this would somewhat offset the variation. Further, the determinations being made by the same machine under the same circumstances, would make the curves reliable from the standpoint that the determinations were made always under the same conditions.

As a whole, there was a definite rise in rate in all cases during the period of about ten to three days before delivery. In some instances

TABLE 1

DAY A.P.	CASE	1	2	3	4	5	6	7	8
	Total Calories per hr.	61.2	69.9		70.0	70.4	62.0	62.9	
14	B.M.R.—%	+ 3.3	+15.9		+20.9	+14.1	+ 3.8	+ 8.9	
	Weight in Kilos	56.7	60.0		55.4	67.0	56.5	61.0	
	Total Calories per hr.	58.1	68.9		69.2	68.4	62.0	60.9	
13	B.M.R.—%	- 2.0	+14.3		+19.4	+10.9	+ 4.1	+ 6.1	
	Weight in Kilos	56.7	60.0		55.5	67.2	56.1	60.3	
	Total Calories per hr.	54.5	69.9		69.8	70.4	62.1	64.2	
12	B.M.R.—%	- 7.9	+15.9		+20.5	+14.2	+ 3.9	+11.5	
	Weight in Kilos	56.7	60.0		55.4	67.3	56.5	60.5	
	Total Calories per hr.	65.1			69.9	69.3	60.9	62.8	
11	B.M.R.—%	+ 9.9			+20.8	+11.7	+ 2.2	+ 8.9	
	Weight in Kilos	57.2			55.7	68.0	55.9	61.0	
	Total Calories per hr.	60.8			68.6		63.7	64.6	
10	B.M.R.—%	+ 2.6			+18.1		+ 6.4	+11.9	
	Weight in Kilos	57.0			55.8		56.9	61.0	
	Total Calories per hr.	60.5	68.9	69.5	67.9	68.8	69.4	63.3	
9	B.M.R.—%	+ 2.2	+14.3	+ 3.8	+17.3	+10.9	+15.8	+ 9.3	
	Weight in Kilos	57.0	60.3	70.5	55.5	68.3	57.4	61.6	
	Total Calories per hr.	60.9		80.0	68.0	67.6	60.5	59.5	
8	B.M.R.—%	+ 2.2		+19.1	+17.5	+ 9.3	- 0.2	+ 2.7	
	Weight in Kilos	57.8		70.8	55.5	67.5	57.9	61.6	
	Total Calories per hr.	59.0	69.7	76.2			65.9	61.7	
7	B.M.R.—%	- 0.9	+15.6	+13.6			+ 9.2	+ 6.9	
	Weight in Kilos	57.6	60.3	70.9			57.6	61.2	
	Total Calories per hr.	60.1	69.3	76.4	71.1	68.2	68.2	63.1	
6	B.M.R.—%	+ 0.9	+14.6	+13.8	+22.8	+10.3	+12.1	+ 8.9	
	Weight in Kilos	57.5	60.5	70.8	55.5	67.5	58.4	61.7	
	Total Calories per hr.		68.2	74.6	72.8	68.3	68.7	68.1	61.4
5	B.M.R.—%		+12.8	+14.0	+11.8	+17.6	+11.0	+12.3	+ 6.0
	Weight in Kilos		60.6	70.8	68.2	56.0	67.5	58.0	61.5
	Total Calories per hr.		74.1		66.9	69.5		66.5	61.6
4	B.M.R.—%		+22.5		+ 2.7	+20.4		+ 9.6	+ 6.3
	Weight in Kilos		60.5		68.0	55.2		58.3	61.6
	Total Calories per hr.	63.4	70.6	72.7	69.8	67.2	69.0	68.1	60.0
3	B.M.R.—%	+ 4.9	+17.8	+11.3	+12.5	+20.4	+13.6	+12.9	+ 3.6
	Weight in Kilos	58.1	60.5	70.5	67.7	55.1	67.7	58.3	61.6
	Total Calories per hr.	63.4	70.6	72.7	69.8	67.2	69.0	68.1	60.0
2	B.M.R.—%	+ 6.2	+16.7	+ 8.9	+ 7.3	+16.1	+11.9	+12.2	+ 3.2
	Weight in Kilos	58.3	60.8	70.4	67.7	55.4	67.3	58.3	61.8
	Total Calories per hr.	61.0	71.2	74.7	63.0	68.7	68.7	66.9	63.0
1	B.M.R.—%	+ 2.4	+17.7	+11.2	- 2.9	+18.7	+11.4	+10.5	+ 8.4
	Weight in Kilos	58.5	60.6	70.4	67.6	55.6	67.3	58.2	62.0
	Labor started in hours:	7	5	12	6	24	6	4	24

TABLE I—CONT'D

DAY P.P.	CASE	1	2	3	4	5	6	7	8	
1	Total Calories per hr.	60.6	64.9	70.0	65.4	52.8	60.5	66.0	55.8	
	B.M.R.—%	+ 4.3	+10.4	+ 8.6	+ 4.1	- 2.9	+ 0.6	+17.5	- 0.3	
	Weight in Kilos	54.5	56.7	64.5	63.0	48.2	62.8	49.3	56.6	
2	Total Calories per hr.	57.1	61.6	68.1	62.4	56.1	54.0	60.4	56.7	
	B.M.R.—%	+ 1.2	+ 5.5	+ 6.3	+ 0.4	+ 2.8	- 9.2	+ 7.5	+ 1.9	
	Weight in Kilos	54.4	56.2	63.6	61.3	48.7	60.8	49.1	55.5	
3	Total Calories per hr.	61.3	59.8	65.6	59.6	54.9	55.3	53.6	55.4	
	B.M.R.—%	+ 6.9	+ 1.9	+ 2.2	- 4.5	+ 0.7	- 6.7	- 4.5	- 0.4	
	Weight in Kilos	53.2	56.4	63.9	61.7	48.6	60.6	48.9	55.0	
4	Total Calories per hr.	59.2	59.2	65.4	64.1	54.9	53.4	52.8	53.7	
	B.M.R.—%	+ 3.2	+ 1.3	+ 1.9	+ 2.6	+ 0.7	- 9.6	- 6.0	- 3.4	
	Weight in Kilos	53.1	56.2	63.9	61.6	47.9	60.3	49.1	55.5	
5	Total Calories per hr.			57.8	65.2	67.5	56.1	53.8	55.3	
	B.M.R.—%			- 1.0	+ 1.9	+ 8.0	- 3.3	- 9.3	- 0.5	
	Weight in Kilos			55.8	63.6	62.0	47.9	60.4	55.7	
6	Total Calories per hr.						52.9	54.1	56.1	
	B.M.R.—%						-10.4	- 3.1	+ 1.2	
	Weight in Kilos						47.8	60.0	48.3	55.5
7	Total Calories per hr.	57.2	57.6	70.1	65.4	51.5	54.1	54.2	53.5	
	B.M.R.—%	+ 0.5	- 0.4	+ 9.5	+ 4.6	- 5.3	- 7.7	- 2.9	- 2.1	
	Weight in Kilos	52.0	54.5	63.4	62.0	47.0	59.5	47.8	54.1	
8	Total Calories per hr.	62.4		69.1	62.8					
	B.M.R.—%	+ 9.4		+ 7.8	+ 0.5					
	Weight in Kilos	52.0		63.5	61.8	46.4				
9	Total Calories per hr.			57.2		64.5	52.8	54.9	49.6	53.1
	B.M.R.—%			- 1.0		+ 3.5	- 1.4	- 7.0	-11.2	- 2.5
	Weight in Kilos			54.7		61.5	46.5	59.8	48.2	53.5
10	Total Calories per hr.	51.9	54.8	64.6		51.9	53.4	50.2	51.8	
	B.M.R.—%	- 8.2	- 4.9	+ 1.1		- 2.9	- 8.4	-10.1	- 4.8	
	Weight in Kilos	51.2	54.3	62.8		46.5	59.2	48.0	53.5	
11	Total Calories per hr.			55.3		58.9		52.3	52.1	
	B.M.R.—%			- 4.1		- 5.4		-10.3	- 4.4	
	Weight in Kilos			54.4		61.4	46.3	59.1	53.5	
12	Total Calories per hr.	57.1	55.4	59.9		50.1		52.5		
	B.M.R.—%	+ 0.8	- 3.8	- 6.1		- 6.5		- 6.2		
	Weight in Kilos	51.3	54.3	63.1		46.3		48.5		
13	Total Calories per hr.	61.2	53.1	59.8			53.6	54.7	48.7	
	B.M.R.—%	+ 8.1	- 8.0	- 6.3			- 8.1	- 2.6	-10.5	
	Weight in Kilos	51.3	54.4	63.0		46.4	59.1	49.2	53.6	
14	Total Calories per hr.					50.7	52.9		47.9	
	B.M.R.—%					- 5.4	- 9.1		-12.0	
	Weight in Kilos					46.4	58.5		53.5	
	Total Calories per hr.				60.1		50.1			
6 wk.	B.M.R.—%				- 5.2		-15.7			
	P.P. Weight in Kilos				63.0		61.0			

this rise was persistent, particularly, to the time of delivery and in several cases there was a definite drop before labor set in. The details can be best studied in Tables I and II.

A marked drop was observed in eight instances, a slight drop in six, and a definite rise in three. (See Table III.) In considering the rate of the fetus the same as the mother, the drops observed do not correspond in any definite way to the actual rate obtained after delivery.

TABLE II

DAY A.P.*	CASE	9	10	11	12	13	14	15	16	17
14	B.M.R.—%			— 9.1	— 7.0	—32.6	—14.8			
	Weight in Kilos			59.0	64.0	64.5	52.0			
13	B.M.R.—%					—21.3	—17.8		— 2.6	
	Weight in Kilos					64.8	52.8		88.0	
12	B.M.R.—%	+10.0			— 9.8	—31.9	—16.3			
	Weight in Kilos	61.5			64.5	64.5	52.0			
11	B.M.R.—%					—29.0	—17.4		— 4.1	
	Weight in Kilos					64.5	53.0		88.5	
10	B.M.R.—%	+ 8.0		+ 8.3	—11.4	—29.4	—13.2		— 5.7	
	Weight in Kilos	62.5		59.0	64.5	64.2	52.0		89.0	
9	B.M.R.—%	+ 9.4		— 5.7						
	Weight in Kilos	62.5		59.0						
8	B.M.R.—%	+13.8		— 6.1	—10.4	—18.4	— 3.1		— 6.6	
	Weight in Kilos	62.0		59.0	64.0	65.0	52.5		89.0	
7	B.M.R.—%		+ 4.3	—17.8				— 3.4		—11.2
	Weight in Kilos		64.0	59.0				60.0		51.5
6	B.M.R.—%	+15.6		— 9.6		—16.2	— 2.2	— 1.6		
	Weight in Kilos	62.0		59.0		64.5	52.5	58.0		
5	B.M.R.—%	+ 8.0	+ 6.9	—16.3	— 9.4	— 9.6	— 6.8		— 9.7	—13.8
	Weight in Kilos	62.0	64.5	59.0	65.0	64.5	52.5		90.0	52.0
4	B.M.R.—%					— 6.5	+ 8.0	— 2.8	— 0.8	
	Weight in Kilos					64.5	52.5	57.5	90.0	
3	B.M.R.—%	— 3.3	+ 1.6	—13.2	— 7.7		+ 5.1		+ 0.2	— 6.4
	Weight in Kilos	62.5	64.0	59.0	65.0		52.5		89.0	51.5
2	B.M.R.—%	— 2.0	+ 6.4	—11.6		— 7.7		— 3.4		— 7.0
	Weight in Kilos	62.5	64.0	59.0		65.0		58.0		52.0
1	B.M.R.—%	+ 1.2	+ 8.0	— 9.9	— 6.4	—12.6	+ 6.4	— 1.8	— 8.6	— 7.0
	Weight in Kilos	62.5	64.0	59.0	65.0	65.0	51.5	57.5	89.0	52.0
DELIVERY										
HR.										
P.P.										
8	B.M.R.—%		+16.2	— 0.4		(12 hr.)	— 6.3	— 3.6	—12.2	
	Weight in Kilos		58.5	58.0			60.0	—49.5	53.0	
32	B.M.R.—%		+11.5			(36 hr.)	— 6.6		(18 hr.)	—11.6
	Weight in Kilos		58.0				58.5		81.0	

\* Antepartum.

TABLE II—CONT'D

DAYSP.P.	CASE	9	10	11	12	13	14	15	16	17
1	B.M.R.—%			-10.8	-7.3				-15.4	
	Weight in Kilos			53.0	59.0				46.5	
2	B.M.R.—%		+ 3.4	-13.6	-8.4		-4.8	-8.3	-20.4	
	Weight in Kilos		58.0	53.0	58.5		49.0	52.0	80.0	
3	B.M.R.—%					-10.1		-20.1	-21.3	
	Weight in Kilos					59.0		80.0	46.5	
4	B.M.R.—%	+ 3.9	+ 8.6		-5.9	-4.7	-6.2	+ 6.1	-23.3	
	Weight in Kilos	57.5	58.0		57.5	58.5	48.0	52.0	80.0	
5	B.M.R.—%	+ 1.4	+ 1.1	-19.5		-10.7		+ 1.6	-17.3	-22.1
	Weight in Kilos	56.5	58.0	52.0		58.5		51.5	80.0	46.5
6	B.M.R.—%	- 3.6	+ 4.4		-11.4			+ 4.2	-22.7	-19.7
	Weight in Kilos	56.5	57.0		57.0			51.0	79.5	46.0
7	B.M.R.—%	- 6.9	+ 2.0	-15.5						
	Weight in Kilos	56.0	56.0	50.0						
8	B.M.R.—%		- 4.8				- 0.3	-11.8	-20.6	
	Weight in Kilos		56.0				50.0	77.5	45.5	
9	B.M.R.—%	- 7.1	- 5.7	-17.8	-10.8			+ 3.5	-12.8	
	Weight in Kilos	56.0	56.0	49.5	56.5			50.5	77.0	
10	B.M.R.—%				-27.1				-20.6	
	Weight in Kilos				57.5				45.0	
11	B.M.R.—%	- 8.9	+ 3.7				- 2.2			
	Weight in Kilos	56.0	56.0				51.0			
12	B.M.R.—%	- 7.6	+ 6.6			-17.9	- 4.1		-27.8	
	Weight in Kilos	56.0	56.5			43.0	51.0		46.0	
13	B.M.R.—%				-19.6		(8 wk.) - 3.9			
	Weight in Kilos				56.5		50.0			

This is true also, but to a less degree, when the rate of the fetus is determined from the average rate that is given for newly born infants which is 27 calories per square meter of body surface.

From these figures, it can be seen that we have found no consistent drop following delivery comparable to the estimated metabolism of the fetus. In a good many instances the drop is entirely insufficient, and in another instance there is actually a rise. It would seem, therefore, if these determinations are approximately correct, that a good many factors must come into play during the period before and after delivery, which might cause such variations. We feel that from some of the determinations, there is actually some evidence of an increased energy production of the mother during pregnancy. We realize very definitely that this is a clinical investigation in which the methods used are only approximate, and from the somewhat varied results, no definite con-

TABLE III

CASE	BEFORE DELIVERY				AFTER DELIVERY				CALCULATION BEFORE DELIVERY								
	CAL. PER HR. S.A.†		B.M.R. PER CENT		CAL. PER HR. S.A.		B.M.R. PER CENT		FETUS AT RATE OF MOTHER		MINUS FETUS		FETUS AT AV. RATE OF NEW-BORN		MINUS FETUS		
	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	CAL. PER HR. S.A.	B.M.R. PER CENT	
1	61.0	+ 2.4	60.6	+ 4.3	7.0	54.0	- 8.3	4.9	56.1	- 4.7	W.P.*						
2	71.2	+17.7	64.9	+10.4	10.0	61.2	+ 4.4	6.0	65.2	+11.2							
3	74.7	+11.2	70.0	+ 8.6	8.9	65.8	+ 0.9	6.0	68.7	+ 5.5	W.P.						
4	63.0	- 2.9	65.4	+ 4.1	7.5	55.5	-12.2	5.7	57.3	- 9.4							
5	68.8	+18.7	52.8	- 2.9	11.5	57.3	+ 2.5	7.0	61.8	+10.6							
6	68.7	+11.4	60.6	+ 0.6	9.8	58.9	- 2.1	6.5	62.2	+ 3.3	W.P.						
7	66.9	+10.4	60.5	+ 7.5	9.5	57.4	- 2.4	6.2	60.7	+ 3.2							
8	63.0	+ 8.4	55.8	- 0.3	7.8	55.2	- 3.1	5.1	57.1	+ 1.6	W.P.						
9	61.6	+ 1.23	68.8	+16.25	7.4	54.2	- 8.3	5.4	56.2	- 4.9							
10	63.2	+ 8.0	56.0	- 0.4	7.7	55.5	- 2.9	5.1	58.0	- 1.6							
11	52.6	- 9.9	49.0	-10.8	7.0	45.6	-20.0	5.7	46.9	-17.0							
12	59.5	- 6.4	56.4	- 7.3	7.7	51.8	-14.4	5.9	53.6	-11.4							
13	59.3	-12.6	61.0	- 6.3	6.6	52.7	-20.0	5.1	54.2	-17.8							
14	57.3	+ 6.4	51.4	- 3.6	8.6	48.7	- 7.2	5.9	51.4	- 2.1							
15	57.2	- 1.8	49.3	-12.2	8.9	48.3	-14.0	6.5	50.7	- 9.8							
16	73.0	- 8.7	67.0	-11.6	9.1	63.9	-18.3	6.7	66.3	-15.2							
17	56.3	- 7.0	49.8	-15.4	7.0	49.3	-16.7	5.1	51.2	-13.5							

\*Without Placenta.

†Surface area.

elusions can be drawn either in regard to an increased energy production of the mother per se during pregnancy or to a stationary one.

We offer these determinations as a preliminary report and make no definite conclusions from our present experiences, but shall reserve these until further data are obtained.

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### CLINICAL STUDY OF POSTOPERATIVE VALUE OF BARBITURIC ACID HYPNOTICS\*

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THIS investigation was undertaken to determine the clinical effects of barbituric acid hypnotics used postoperatively in 471 gynecologic patients subjected to laparotomies and to evaluate their efficiency as substitutes for opium derivatives.

The discoveries of Pasteur in the field of bacteriology, the recognition of the principle of antisepsis by Lister and the boon of anesthesia established the Renaissance in surgery. Despite the range and development of modern operative therapeutics, surgical hazards have been tremendously reduced by the standardization and improvement of technic, and by an appreciation of underlying basic principles. Yet the acknowledgement that operative risks do exist has served as a challenge and stimulus to medical research and scientific investigation, reflected in the acquisition of new facts which have further safeguarded the patient. The discovery of insulin has revolutionized the medical and surgical treatment and prognosis of the diabetic, the recognition of the value of iodine in the preparation of the toxic exophthalmic patient has eliminated one of the great surgical problems, and the rôle of calcium in preventing hemorrhage has given the surgeon a sense of security when operating upon the jaundiced patient. Examples possibly less dramatic but none the less significant are the modifications of the preoperative preparation of the individual. The universal custom of purging and starving for several days before operation has been supplanted by a more rational attitude based upon the demands of physiologic function. Intestinal

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peristalsis is disturbed by catharsis and alteration of bowel function is followed by ileus and distention. The necessity for the preoperative administration of fluid and food (especially carbohydrates) is apparent when we consider the important rôle of tissue water-balance and acid-base equilibrium in normal function. Recent advances in the field of anesthesia indicate that the search for the ideal anesthetic continues and suggest that important developments may be looked for in that direction. This investigation was stimulated by a dissatisfaction with the postoperative effects of opiates which developed because of the pharmacodynamic action of the drugs.

*Preoperative Preparation.*—The keynote of preoperative preparation is prophylaxis and, to minimize surgical risk, attention is directed to the study of the individual's functional capacity, and the correction of unfavorable modifying factors which might lead to postoperative complications. Briefly, it includes a complete physical examination, uranalysis, kidney function tests, blood count, Wassermann, sedimentation and blood pressure readings. Any variation from the normal standards demands further investigation or corrective therapy. A liberal diet is given and water and high calorie fruit juices are forced until a few hours before the actual operation. Berwick's dye (aleoholic solution of brilliant green-crystal violet) is applied to the gums to fortify oral hygiene, and physical and psychic rest is assured during the night preceding surgery by administering sedatives or hypnotics. An enema the morning of operation is routine.

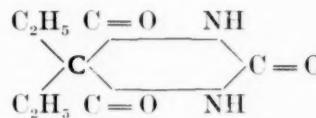
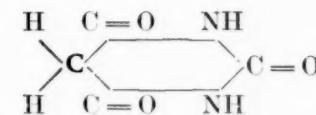
Long-established custom has sanctioned the use of opiates for pre-anesthetic hypnosis for the purpose of depressing the general metabolic level to facilitate the induction and administration of the anesthetic, and to relieve the apprehension incident to the anesthetic itself. The rationality of preanesthetic opiates must be questioned, however, when we review some of the undesirable effects which follow the use of morphine and allied drugs. The respiratory depression, the disturbance of metabolism, and the occasional excitement which occurs after opiates must suggest that they are not the ideal or necessary adjuncts to anesthesia. Recently we have substituted barbiturates to secure preanesthetic hypnosis, with entirely satisfactory results.

*Postoperative Care.*—Following operation, the immediate concern of the surgeon is the maintenance of body heat, the restoration of fluids lost by skin evaporation or hemorrhage, the stimulation of the organs of elimination, and the relief of pain. Our interest was especially centered in the latter. Pain after laparotomy is inevitably present, due to the operative procedure itself, and though there is a marked individual and racial variation in pain threshold, it is of vital importance to reduce discomfort to a minimum. From this standpoint, opiates have been the most valuable drugs in the pharmacopeia, for unquestionably they do alleviate pain; however, their use is also attended with undesirable fea-

tures which definitely increase the possibility of postoperative complications. Intestinal motility is always depressed by abdominal procedures and opiates, because of their inhibitory action on peristalsis, increase bowel atony and distention. Moreover, intestinal stasis favors the rapid development of gas-forming organisms, which further complicates the picture. It is generally agreed that disturbance of the acid-base balance occurs after a general anesthetic, and opiates, by virtue of their action on the vomiting center, further increase acidosis. The depression of the respiratory center after morphine results in slower elimination of the anesthetic, and lessened pulmonary ventilation which favors atelectasis and, finally, idiosyncrasy is not uncommon and manifests itself by excitement and sleeplessness. These criticisms seemed valid reasons for investigating substitutes against which such objections could not be raised and yet which were effective in controlling postoperative discomfort. To be acceptable, the therapeutic agent must necessarily meet certain standards; namely, 1. A wide margin of safety between the medicinal and toxic dose; 2. Ability to relieve pain and induce sleep. 3. No effect on vital functions. 4. Prompt elimination.

*Hypnotic Drugs.*—Hypnotics, because of their specific effect upon the psychic centers, seemed a logical choice. These drugs, except hyoscine, are synthetic compounds which vary in chemical composition; their somnifacient action is enhanced by certain chemical groups. Ketone and aldehyde linkings are often found, ethyl and propyl side-chains are usual, and while halogen compounds increase the hypnotic effect, circulatory depression is more marked. Synthetic hypnotics may be classified as follows: 1, polymeric aldehydes (paraldehyde), unpleasant because of disagreeable aftertaste and breath; 2, di-ethyl sulphones (sulphomethane), dangerous action on kidney and slow and uncertain absorption; 3, carbamates (hedonal), too weak; 4, halogen compounds (chloral), too depressing to heart and circulation; 5, malonyl-urea derivatives (barbital, etc.), satisfactory from a pharmacologic viewpoint.

*Barbiturate Acid Compounds.*—Barbituric acid has the following chemical structure:



The addition of two ethyl radieals to the di-ethyl malonyl urea produces barbital. This drug (trade name "veronal") was introduced in 1903 and since then many modifications of the original substance have

been exploited. The substitution of phenyl, allyl, propyl, butyl, etc., for the ethyl radical enhances the hypnotic action but at the same time increases the toxicity of the preparation. Phenobarbital ("luminal"), di-allyl barbituric acid ("dial"), iso-amyl-ethyl barbituric acid ("amytal") are some representatives of such modifications.

Barbiturates are not soluble in water except when prepared as alkaline salts but are readily absorbed from the stomach. A small proportion is destroyed in the body but the greater part is eliminated unchanged in the urine within ten to twenty-four hours. There may be cumulative effect. The systemic action is practically limited to the central nervous system, particularly the brain and cord; the peripheral sensory and motor nerves are undisturbed. The sensory cortex is more depressed than the motor, except after phenobarbital ("luminal"), which has a selective depressant action on the latter. Reflexes are disturbed before the pain sense. Special senses are rarely altered, although at times there may be papillary dilatation and loss of light reflex. Even in toxic doses, there is no disturbance of the digestive function. The blood is not altered, the heart is not influenced. Peripheral blood vessel dilatation may occur, leading to sweating which may cause cutaneous lesions, especially on the face; but this dilatation is not dependent upon paralysis of the arterioles, as shown by typical ephedrine response.

Toxic symptoms are manifested by periods of motor excitement, muscle twitching and ataxia, followed by shallow periodic respirations and coma. Lethal doses cause respiratory paralysis, and postmortem examination shows dilatation of the heart, congestion of the brain and viscera, and edema of the lungs.

Studies of the effect of barbituric acid hypnotics in human subjects (Anderson, Chen, Leake) showed that "barbital, ipral, neonal, and phandoform tend to reduce oxygen consumption and tactile discrimination. Amytal and phenobarbital tend to increase oxygen consumption except in relatively high dosage. Barbital seemed more universally depressing than its common derivatives, not only on basal rate and attention, but also on pulse rate and blood pressure." Barbiturates are essentially sleep-producing drugs and are not analgesics except in large doses.

To determine the value of these hypnotics after operation, it seemed rational to combine them with an agent specifically analgesic. Experimental evidence has indicated that amidopyrine acts synergistically with the barbiturates (Van Noorden) and that mutual antagonism in the toxic action of each agent exists (Starkenstein, Kaer and Loewe). Allyl-iso-propyl barbituric acid and amidopyrine (Allonal) was first studied from this standpoint. This preparation, dispensed in 0.15 grams (2- $\frac{1}{3}$  grain) tablets is a loose chemical combination of a hypnotic and analgesic in the proportion of 1:1.66.

*Technic of Administration.*—Four tablets (0.6 grams) of the drug were crushed and given by mouth in a small amount of water as soon as

postoperative nausea had ceased. When the patient began to arouse, usually five or six hours later, the same dosage was repeated; and, depending upon the indications, a similar amount was repeated usually eight hours later. Subsequent dosages were reduced to 0.3 grams and were given when pain and sleeplessness indicated that the effects of the medication were wearing off. Individualization and experience facilitated the recognition of the need for further medication. However, in all cases it was discontinued on the third day after operation. In some cases, four grams of sodium bromide in a retention enema were given as soon as the patient returned from the operating room, and was repeated in six hours. A review of our data indicates that the bromide was a partial but not a necessary adjunct to the barbiturate. Because we appreciate the difficulties of medication by mouth after a general anesthetic, we employed this method of administration as offering a more rigid test for evaluating the medication and important in eliminating any psychic element incident to hypodermic injection.

Two and one-half to three liters of normal salt solution were given by hypodermoclysis when the patient returned from the operating room, and warm water by mouth was forced as soon as fluids were tolerated. The hypodermoclysis was repeated or intravenous glucose was given when it was deemed necessary. If the patient was unable to urinate after twelve hours, the bladder was catheterized followed by an instillation of silver nitrate solution. To avoid retention, after voiding, the catheter was used until it was demonstrated that there was less than 30 c.c. of residual urine in the bladder. On the third postoperative day, an enema was given and the patient was usually on a light diet.

*Reaction to Allonal.*—Within one hour after the first dose of allonal had been given, there was definite control of pain and often sleep ensued. Subsequent medication was followed by several hours of quiet sleep or periods of sleep interrupted by restlessness or delirium. Occasionally, restlessness prevented sleep. The importance of protecting the patient during these often sudden onsets of delirium was forcibly emphasized in the early part of this investigation when several patients attempted to or actually climbed out of bed. This need was successfully met by attaching high canvas frames to the sides of the bed. Subsequent questioning of the women often revealed an underlying factor of financial worries or home difficulties which probably offered an unfavorable modifying background. The neurotic or highly nervous person was more prone to delirium; Orientals and the phlegmatic type were usually placid and relaxed. On the other hand, we soon learned to recognize that delirium appearing after forty-eight hours of medication indicated an overdosage of the drug and increasing experience enabled us to gauge the dosage so as to avoid this complication. At times, thickness of speech or inability to swallow liquids was noted, undoubtedly the result of muscle incoordination. Complete recovery from the nar-

cosis was apparent within twelve to twenty-four hours after the medication terminated. Blurred vision or diplopia was occasionally present during this phase. During the period of "allonal narcosis," the temperature, pulse, and respiratory rate were carefully observed, special emphasis was placed upon the frequency and severity of postanesthetic vomiting, distention, or any complication which could be attributed to the medication.

#### ALLONAL SERIES, 381 PATIENTS

Allonal was used postoperatively in 381 women, all of whom had laparotomies. Because we considered that control of pain incident to abdominal surgery would offer a more crucial test of the efficiency of the drug, we have not included in this report any patients having only a vaginal plastic operation, for there is rarely marked discomfort in this group.

The operative procedures are shown in Table I.

TABLE I. ALLONAL SERIES—381 PATIENTS

Hysterectomy	159
Suspension uterus	90
Cesarean section	26
Myomectomy	9
Salpingo-oophorectomy	97

These operations were indicated for the treatment of uterine and ovarian cancers, fibroids, uterine displacements, inflammatory disease or tumors of the adnexa, endometriosis, and pregnancy. Vaginal and cervical repairs and appendectomy were done when it was indicated.

144 women received allonal alone after operation	(All.)
77 women received allonal and one hypodermic of opiate	(All.0 <sup>1</sup> )
81 women received allonal and two hypodermics of opiate	(All.0 <sup>2</sup> )
79 women received allonal and three hypodermics of opiate	(All.0 <sup>3</sup> )

Opiates were given once or twice because immediate postoperative nausea prevented mouth medication or because the patient's restlessness interfered with the comfort of other ward patients. The indications for three or more hypodermics are shown in Table II:

TABLE II

Excitement after allonal narcosis	28
Excitement during allonal narcosis	24
Vomiting	17
Opiates preceded allonal	7
Postoperative pneumonia	2
Morphine addiction	1
	—
	79

Opiates could probably have been eliminated, except in the group (52) of women who were excited from an overdose of hypnotic and in the

morphine addiet, by hypodermic administration of the hypnotic. However, we felt that the subgroups which were based upon the number of opiate hypodermies might offer an interesting basis of comparison with the group in which no opiates were given.

In any discussion of postoperative nausea and vomiting, certain factors must be considered; namely, individual susceptibility, type and duration of anesthetic, and local irritation. With the exception of the 26 pregnant women delivered by cesarean section under nitrous oxide, the anesthetic agent was ether. Ether is more likely to cause nausea and vomiting than are nitrous oxide or ethylene; and, while there was no vomiting in 65 per cent of the cases, it is probably fair to attribute the

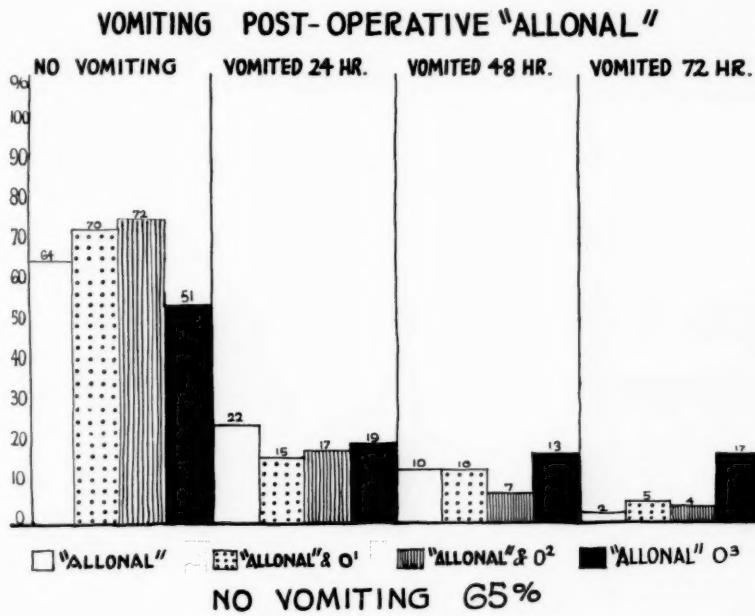


Fig. 1.

vomiting within twenty-four hours after operation to the anesthetic itself. While a few patients who received no opiates vomited on the second and third postoperative days, in no case was the vomiting severe nor did it require treatment. In the group with one hypodermic of narcotic (allonal O<sup>1</sup>), lavage was done in 2 patients who vomited after the first day. Lavage was required 3 times in the "allonal O<sup>2</sup>" group, 2 of these patients having acute dilatation of the stomach and being distended; the third patient vomited several times but was not distended. In the "allonal O<sup>3</sup>" group, 9 patients were treated with lavage for marked vomiting; all had considerable distention. A consideration of the frequency of vomiting occurring after twenty-four hours, when presumably the effects of the anesthetic had worn off, shows that it was twice as frequent in the "allonal O<sup>3</sup>" group (30 per cent as in the other

three subgroups (12 per cent, 15 per cent, 11 per cent), yet the various operative procedures were practically identical in each group. While perhaps these differences are not striking, they must suggest that opiates played a part in the prolonged vomiting.

**Distention.**—Distention is a troublesome and possibly unavoidable concomitant of abdominal operations. The recognition of some factors which predispose to its development, namely, operative tissue trauma, cooling and drying of the intestines, traction of mesenteric supports, has developed the principles of sharp dissection, warm moist rubber dams to wall off intestines, and adequate exposure of the operative field. The frequency of distention is shown in Fig. 2.

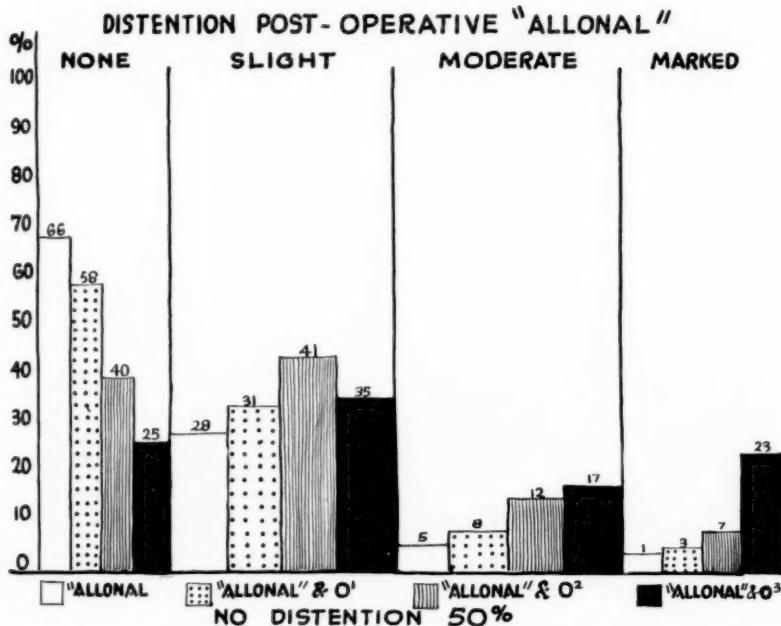


Fig. 2.

In the entire series, 50 per cent of the cases had no distention whatever and only 7 per cent had marked distention. In analyzing the subgroups, we find that two-thirds of the patients having allonal only, had no distention; but as the number of opiates increased, there were steadily fewer patients who were free from distention. Only 1 per cent of the women in the allonal (without opiates) group had marked distention; this incidence steadily rose in the other groups and was present in 23 per cent of the "allonal O<sup>3</sup>" division. These findings definitely indicate that opiates depress postoperative peristalsis and influence the frequency and degree of bowel atony after operation.

Until recently, medical progress has been so occupied with the application of biology, chemistry, and physics to the welfare of human beings

that the effect of the psychic influence upon organic function has been often overlooked. The current interest in "proper mental attitude" to the operative ordeal and the development of the "psychoanesthetists" suggests a readjustment of this attitude and an appreciation of the close interrelationship between the individual's organic and psychic determinants. Every surgeon realizes that the "recovery phase" of surgery may be a period of real stress and strain and amnesia, for events at this time would be a boon which by eliminating psychic trauma, would favorably influence the patient's recovery.

### DOSAGE "ALLONAL" IN MGM. PER KILO

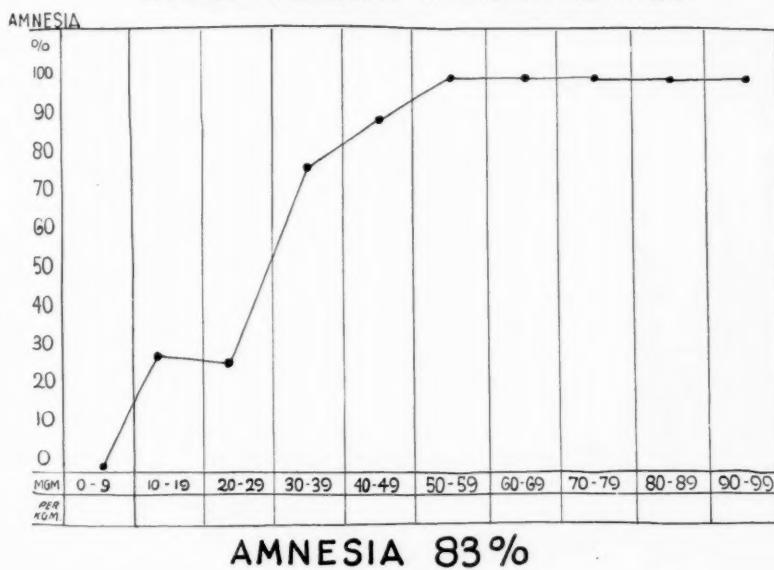


FIG. 3.

Allonal	144 cases	86.0% (128)
Allonal 01	77 cases	84.4% (65)
Allonal 02	81 cases	82.7% (67)
Allonal 03	79 cases	72.1% (57)
* 83.3%		

*Amnesia.*—The hypnosis following allonal strongly resembled a twilight sleep effect. While the patient was usually cooperative, appreciation of the time interval was entirely disorganized and the memory for events or pain was lost. After recovery from the hypnosis, it was often difficult to convince the patient that several days had elapsed since the operation, yet the evident relief when the situation was realized served as a valuable index of the degree of apprehension with which the operation and its sequelae had been approached. We consider that amnesia obtained by the barbiturates is a strong recommendation for their use.

**Dosage.**—Dosage was determined by body weight and is expressed in milligrams per kilo. The majority of the patients were in the third, fourth, and fifth decades, the youngest was twenty-three years, the oldest seventy years.

The range of dosage indicates the wide margin of safety of the preparation. With less than 30 mg. (total dosage per kilo) of the drug, amnesia followed in one quarter of the patients, which suggests inadequate dosage. Two hundred and sixteen patients (56.6 per cent) received between 40-50 mg. per kilo; quiet sleep followed in 73 per cent and amnesia in 83 per cent; therefore, we considered this the ideal dosage. While larger doses were followed by amnesia in every case,

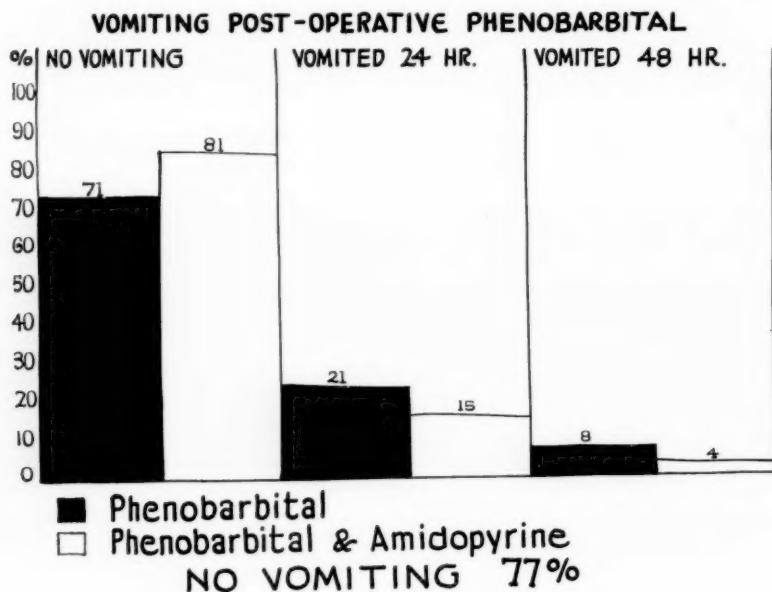


Fig. 4.

the incidence of excitement or delirium increased, probably being toxic manifestations from overdosage. These large doses were given during the early part of the study before we had any basis for comparison for dose standardization.

Although we were encouraged with the results obtained by allonal, we were also impressed with the validity of the criticism offered against a preparation in which the analgesic and hypnotic constituents were combined in fixed proportion; moreover, in such combinations, cumulative action of the more slowly eliminated agent (hypnotic) might lead to overconcentration and toxic manifestations. Unfortunately, the quantitative recovery of barbiturates in the urine is a time-consuming and rather technical procedure. Following the lead of investigations (Kopppanyi and Lieberson) on the difference of rate of elimination of amido-

pyrine and barbiturates in animals, attention was now directed toward the clinical effects observed, following the use of barbiturates of simpler chemical formulas and amidopyrine; both agents being given separately and according to requirements. The reappearance of pain or sleeplessness was regarded as evidence that the analgesic or hypnotic element was of insufficient concentration in the tissues; presumably because of its elimination, and this indirect method served as an estimate of the relative rate of elimination of each drug.

A small group of women were given either barbital (veronal), phenobarbital (luminal), isoamylethyl barbituric acid (amytal) and amidopyrine postoperatively. The indication for either the hypnotic or analgesic

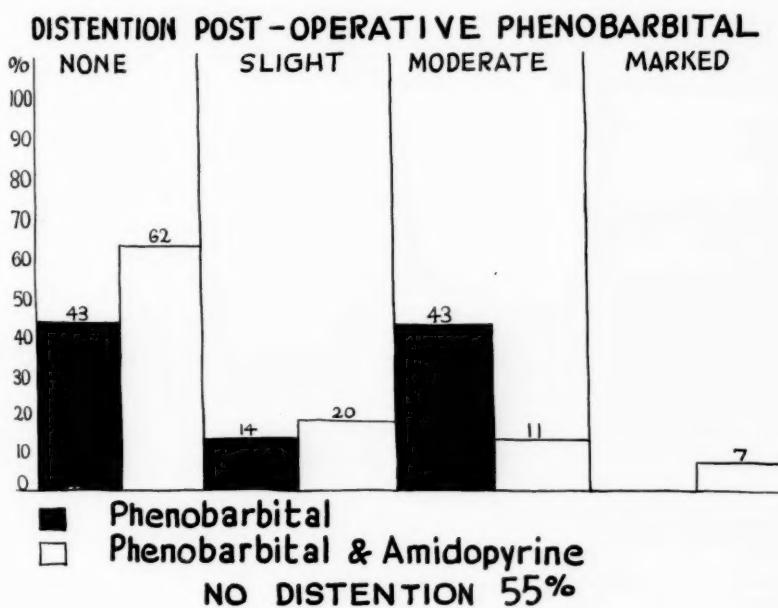


Fig. 5.

agent was determined by the presence of pain or sleeplessness and either or both were repeated according to these indications. Medication was by mouth, and, as in the allonal group, was begun as soon as nausea permitted. The anesthetic and postoperative care were the same as in the previous study.

TABLE III. PHENOBARBITAL—40 PATIENTS

Hysterectomy	28
Myomectomy	1
Salpingo-oophorectomy	4
Suspension	7

I. Phenobarbital was used without an analgesic in 14 cases.  
II. Phenobarbital and amidopyrine were used in 26 cases.

In 4 (28 per cent) of the 14 patients who received the hypnotic without the analgesie, it was necessary to use opiates; in 3 of these women, the dose of phenobarbital was small and there was considerable pain, in the fourth there was excitement after a very large dose of the hypnotic. The one patient of this group who vomited for forty-eight hours had a dilated stomach; she had received opiates.

Opiates were used in 4 (15 per cent) of the 26 patients who received phenobarbital and amidopyrine; three times to relieve pain after inadequate dosage of analgesie and hypnotic, and once to control excitement from an overdosage. The one woman who vomited for forty-eight hours had had opiates.

#### DOSAGE PHENOBARBITAL IN MGM. PER KILO

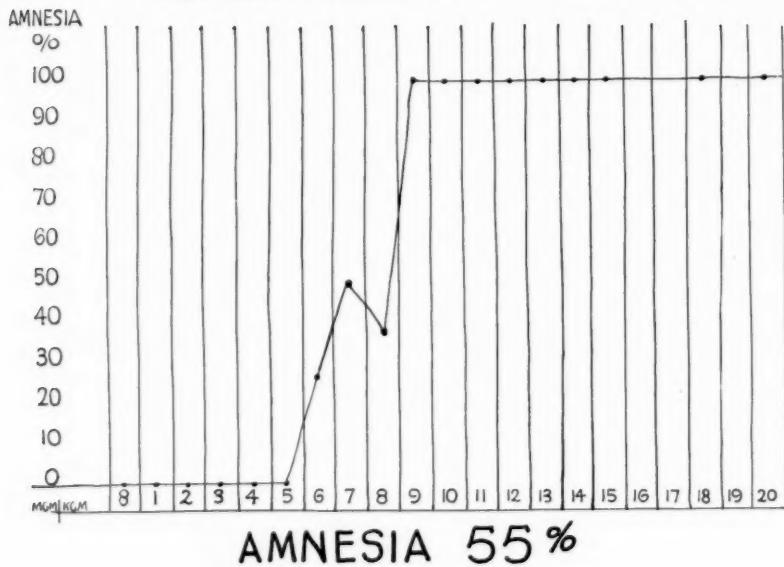


Fig. 6.

Six of the 9 patients having moderate distention received opiates, as did the 2 patients who had marked distention.

While this group of 40 patients is too small to warrant drawing conclusions, it would appear that the incidence of vomiting and distention was definitely increased by opium derivatives. (Fig. 6.) Amnesia occurred in 55 per cent of cases.

Phenobarbital in doses under 5 mg. per kilo was inadequate, required opiates, and was not followed by amnesia. Nine to ten mg. of phenobarbital seemed the proper dose, for quiet sleep and amnesia occurred in every case. Doses higher than 15 mg. per kilo, while followed by amnesia, were often accompanied by excitement. There were no complications that could be attributed to the medication, except skin rashes which occurred three times.

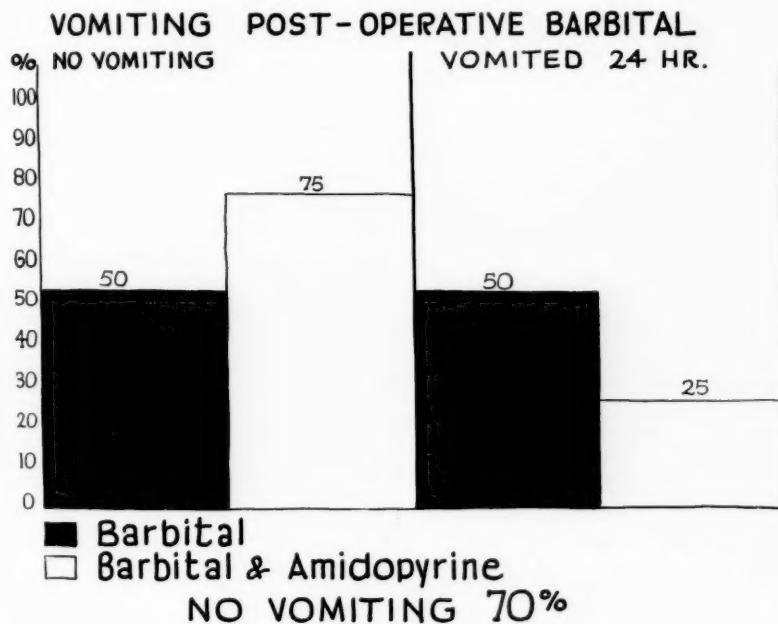


Fig. 7.

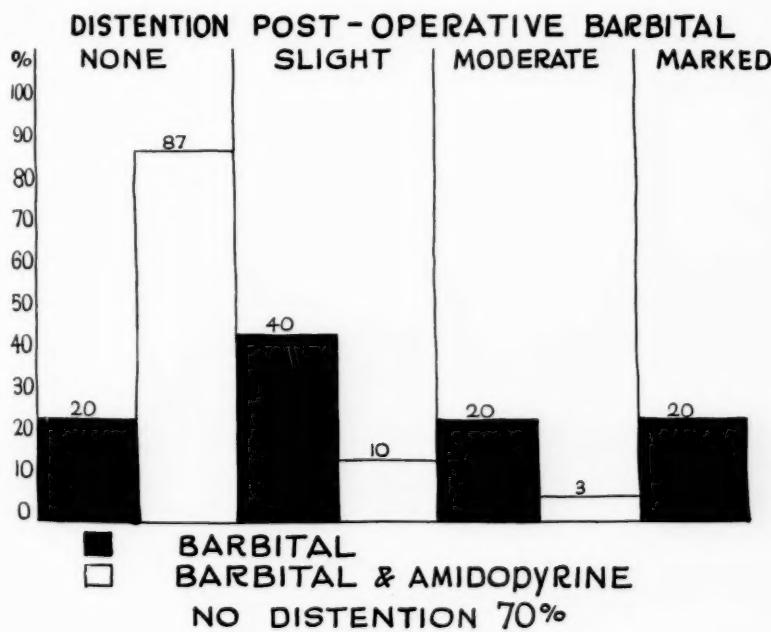


Fig. 8.

TABLE IV. BARBITAL—40 PATIENTS

Hysterectomy	23
Cesarean section (1 Porro)	3
Suspension	5
Salpingo-oophorectomy	9

In this group of cases, barbital and amidopyrine were given according to indications, as outlined in the previous section.

Barbital was used without an analgesic in 10 cases. Barbital was used in combination with amidopyrine in 30 cases.

Barbital alone after operation was not satisfactory and in all instances required supplementary opiates; there was no vomiting in 50 of the

#### DOSAGE BARBITAL IN MGM. PER KILO

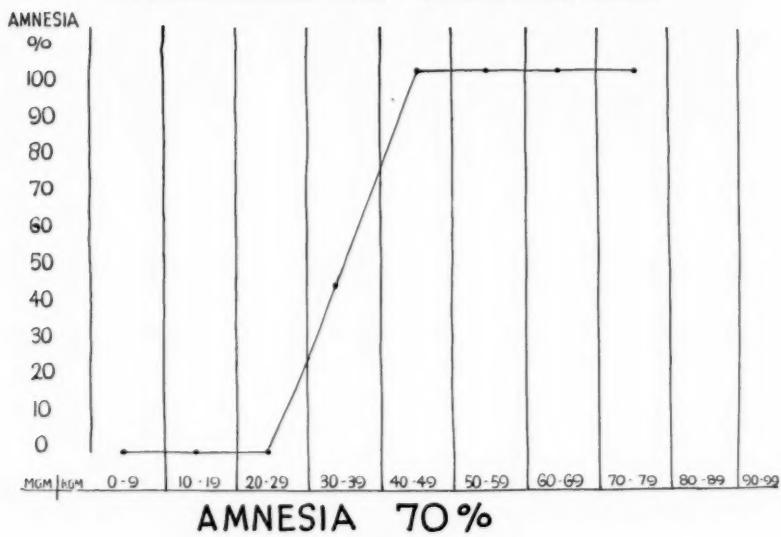


Fig. 9.

patients in this group. Barbital and amidopyrine were a most satisfactory combination, for there were no opiates required and there was no vomiting in 75 per cent of the patients. While the number of cases is small, the above data suggest the advantage of combining the hypnotic with an analgesic agent and indicate the disadvantage of using narcotics postoperatively.

There was no distention in 87 per cent of the cases having barbital and amidopyrine without opiates, whereas there was no distention in but 20 per cent of the patients who had barbital and opiates and in 20 per cent it was marked.

In 5 patients not included in this study, amidopyrine was used postoperatively without an hypnotic; it was found to be inadequate and required supplementary opiates.

Seventy per cent of the patients in this series had amnesia. Forty to fifty mg. of barbital per kilo were followed by quiet sleep and amnesia

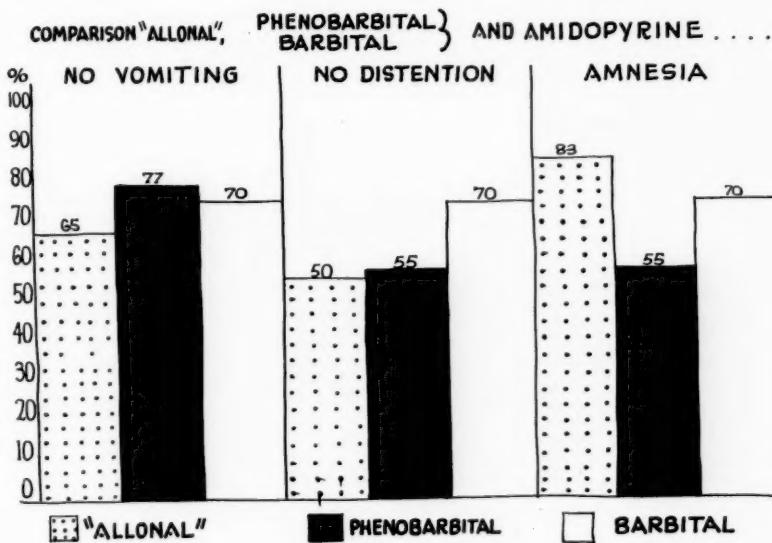


FIG. 10.

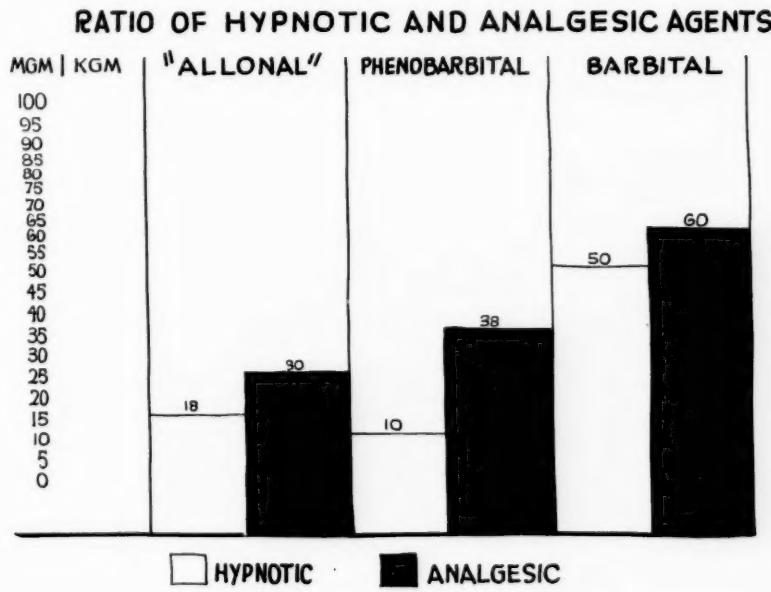


FIG. 11.

in all cases. Larger doses tended to cause delirium, while doses under 40 mg. per kilo did not invariably produce loss of memory.

In a group of 10 patients amytal was used postoperatively with amidopyrine.

Depression was more marked in all cases, and recovery from the hypnosis was more prolonged than with the other barbiturates. However, no conclusions can be drawn regarding the relative value of this hypnotic until further observations have been made.

Comparisons were made between the clinical effects obtained by the allyl-isopropyl barbituric acid combined in fixed proportion with amidopyrine (allonal), and barbital, phenobarbital, and amidopyrine given separately and according to indications.

Because of the difference in the number of cases included in the various groups, absolute conclusions cannot be drawn. However, it would seem that the hypnotic barbital given with amidopyrine when indicated, is a very effective combination. Moreover, because of its relatively simple chemical structure, barbital is definitely less toxic than the other modifications of malynol-urea and is unquestionably less expensive.

*Total Dosage of Hypnotic.*—The *ideal* dosages, as determined by our clinical results, were found to be from 40 to 50 mg. per kilo for allonal, from 9 to 10 mg. per kilo for phenobarbital, and from 40 to 50 mg. per kilo for barbital. The actual dose of hypnotic, however, in the allonal group was but 37.5 per cent of the total dosage, because of the fixed combination with amidopyrine. The coefficients of therapeutic efficiency in these modifications, therefore, are allonal from 15 to 18 mg. per kilo, phenobarbital from 9 to 10 mg. per kilo, and barbital from 40 to 50 mg. per kilo.

*Total Dosage of Analgesic.*—The amount of analgesic in the *ideal* dose of allonal was 25 to 31 mg. per kilo; whereas, when amidopyrine was given alone for clinical indications, the usual dosage was 38 mg. per kilo (range from 20 to 80) with phenobarbital, and 60 mg. (range from 20 to 120) with barbital.

#### DISCUSSION

To complete this investigation, detailed studies of phenolsulphonephthalein readings, blood pressure, blood plasma, carbon-dioxide tension, blood sugar, blood nonprotein nitrogen, and basal metabolic rate were made before and after operation in a group of 20 patients, 5 of whom had had allonal, phenobarbital, barbital, and amytal, respectively. There were no striking or constant changes noted in these preoperative and postoperative determinations, except in the basal metabolic rate which was definitely lowered postoperatively (general average 10 points) with each one of these preparations. Observations made at half-hour intervals for two hours after the administration of these drugs showed, as a rule, that the respiratory rate was slightly increased, but the blood pressure and the pulse rate were generally a little lowered. Reflexes were not disturbed. The urinary output in all cases was commensurate with the fluid intake. Traces of acetone were fairly common in daily urine examinations for the first few days after operation.

There were no postoperative complications that could be attributed to the medication, except for a transient drug dermatitis that occurred in 3 patients who had received phenobarbital. There was no mortality in the entire series.

In the group of women who received the hypnotic and analgesic according to clinical indications, the data suggested a considerable difference in the rate of eliminations of these agents. As a rule, the analgesic required repetition in from six to eight hours, whereas, after the hypnotic effect had once been established, further medication was not necessary, before a twelve- to fifteen-hour interval. This difference in elimination rate emphasized the rational of giving these preparations separately, and supports the therapeutic maxim of drug administration based solely on clinical indications.

We consider that barbituric acid hypnotics in this study were subjected to a most critical test, because of the well-recognized difficulties of oral therapy after a general anesthetic. Undoubtedly, our results would have been more strikingly satisfactory had the barbiturates been administered in solution hypodermically. Despite this handicap, however, we consider that the value of these hypnotics postoperatively has been definitely established.

#### CONCLUSIONS

Opium and its derivatives increase the frequency and severity of postoperative distention and vomiting, and are not necessary to relieve pain. Barbituric acid hypnotics are satisfactory from a pharmacologic and clinical standpoint when combined with an analgesic (amidopyrine). It is illogical to combine these agents in fixed proportion, because of the marked difference in their rate of elimination; it is rational to administer them separately according to clinical indications. Barbital, by virtue of its simple chemical structure, is less toxic and clinically as effective as its more complex and toxic modifications.

We recommend these hypnotics because their action is limited to the central nervous system, their use is followed by a high incidence of amnesia and by little disturbance of organic function.

The author wishes to express her appreciation of the helpful suggestions offered by Dr. Chauncey D. Leake, Professor of Pharmacology, University of California Medical School.

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## PREVENTION AND REPAIR OF HERNIA IN LOW MEDIAN-LINE INCISIONS\*

BY JAMES C. MASSON, M.D., ROCHESTER, MINN.

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I HAVE come to the conclusion that incisional hernia occurs more frequently than most surgeons realize. From 1928 to 1930 operation was performed at The Mayo Clinic on 313 patients for this condition. Unless the hernia becomes enormous or causes distress the patients seldom complain. If patients are obese, hernia is likely to develop not only on account of the increased intraabdominal pressure, but because of the poor quality of the tissues that are brought together.

A predisposing cause of hernia in many cases is a previously infected wound, but hernia may develop in a low median-line scar in cases in which there has been no preceding infection. The cause of the hernia must be the type of incision, type of closure, care following operation, contraction of the abdominal muscles or increase in intraabdominal pressure. Fig. 1 shows the normal condition of the abdomen and the condition which commonly exists in women past middle age who have borne many children. If the abdominal wall is normal, there is little danger of later trouble, if ordinary care is taken in closing the incision, and if a complicating infection and increased intraabdominal pressure are not present. The patient should be kept in bed from ten to fourteen days. When marked diastasis recti abdominis is present and the abdominal wall is pendulous, however, special care must be taken. Approximation of the cut tissues is not enough as they are already stretched and have a relatively poor blood supply; even if healing takes place by primary union the scar that results will soon stretch into a wide weak line of union. In many cases, however, healing will not be satisfactory throughout the entire length of the wound and even when apparently infection or drainage has not occurred, some of the stitches will cut and a piece of omentum or a loop of bowel will enter the wound as the apex of a wedge and gradually spread the wound in the fascia. The peritoneum will gradually grow over the protruding viscera and a true hernia will result.

There is no doubt that in many radical operations for malignant conditions and in cases in which operation is absolutely necessary, the development of a weak line of union or hernia is of slight significance; the indication in such cases is to open the abdomen quickly, and, after the necessary operation, in the peritoneal cavity, to make as

\*Read at the Fifty-sixth Annual Meeting of the American Gynecological Society, Hot Springs, Virginia, May 18-20, 1931.

rapid a closure as possible even at the risk of hernia resulting, and the possible necessity of a secondary operation. Modern methods of operating and anesthesia, however, make the necessity for such incomplete operations relatively few, as practically any surgical procedure can be completed in an hour or the procedure can be changed so that operation may be completed in two or more stages, each of which will be relatively safe. The comparatively low mortality of the present time is probably due in a large measure to careful preoperative preparation, proper selection or proper combination of anesthetics and efficient postoperative care. Only a few years ago many patients died from pneumonia following operation; this rarely occurs now. On the gynecologic service at The Mayo Clinic there were 3,560 operations performed last year with only one death that might in any way be at-

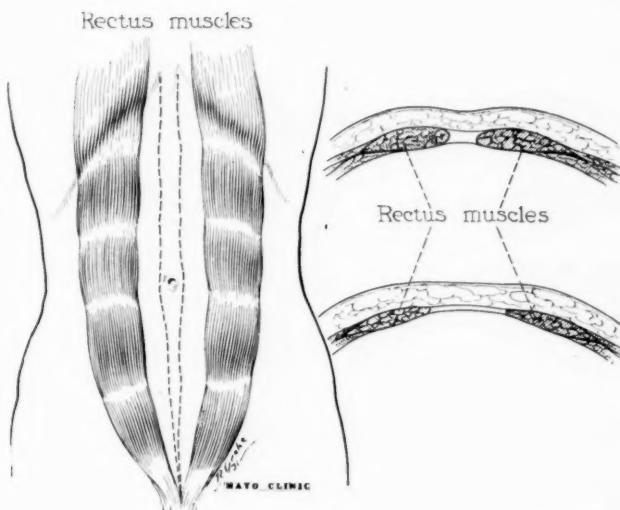


Fig. 1.—Normal rectus muscles and position of muscles in marked diastasis recti abdominis.

tributed to the anesthetic; in that case a spinal anesthetic of *a*-butyloxy-cinehoninic acid diethylene-diamidehydrochloride (nupercaine) was used. There is probably a field for the use of this drug when a long operation is indicated, but I am of the belief that it is more dangerous to use than any of the modern combinations of general anesthetics, spinal anesthetics, local infiltration, or regional block with procaine. When the hernia is large, spinal anesthesia is preferred. This, probably, is about the only operation in which spinal anesthesia is of advantage to both the surgeon and the patient. In many abdominal operations spinal anesthesia is of distinct advantage to the surgeon as it improves exposure, but the end-results in similar operations under a properly selected and properly given general anesthetic are as good if not better.

When making the incision, it is advisable to consider the type of closure, and I am sure that in some cases poor closure results from the fact that a busy surgeon frequently makes the incision thinking only of adequate exposure; after completing the major part of the operation he leaves the closure to an assistant who is anxious to get a reputation as a fast worker and, as a result, approximates the cut structures in a more or less anatomic manner, using relatively few stitches. This is satisfactory in most cases if one is dealing with a practically normal abdominal wall, but in the relaxed, thin wall, it invites or predisposes to postoperative hernia.

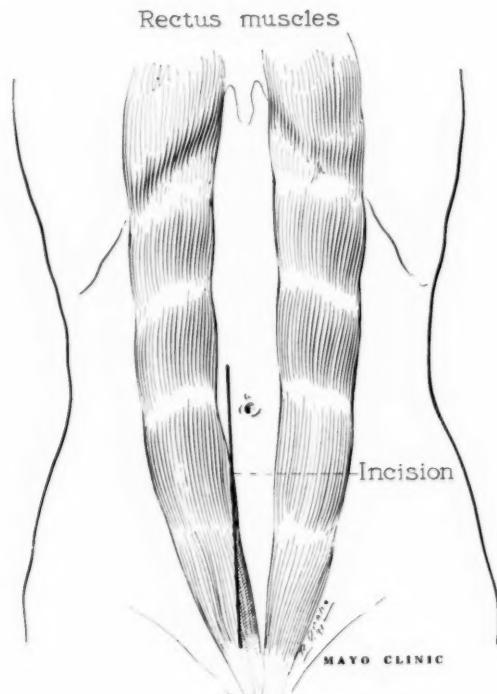


Fig. 2.—Poor type of incision, cutting edge of rectus muscle.

I believe that all incisions for exposure of the pelvis should be in the median line. A dangerous type of incision is one close to the median line through either the right or the left rectus muscle (Fig. 2). When such a wound is closed the narrow mesial strip of muscle has a definite tendency to atrophy, and a weak line of union results. In case the incision is carried above the umbilicus it is generally impossible to approximate the two recti muscles at this level. It is therefore advisable, either to remove the umbilicus or to cut it free from the fascia of the recti, and then to overlap the fascia for a short distance (Fig. 3). If diastasis recti abdominis is not marked the sheath of the rectus should be opened on each side to allow muscle to muscle approximation

and adequate exposure of the external sheath should be made to allow slight overlapping free from adipose tissue. It is much easier to do this before opening through the fascia than at the time of closure. The peritoneum varies a great deal in different cases, but is especially thin and friable if patients are obese. If possible, closure should be made with a running mattress suture and by eversion of the edges, but in many cases, especially if the muscles are not completely relaxed, it

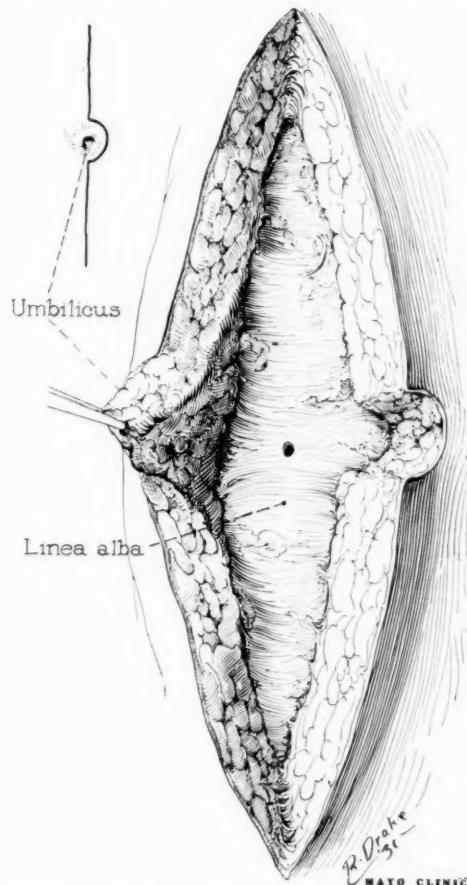


Fig. 3.—Incision extending above the umbilicus; the umbilicus is freed from the linea alba.

may be advisable to close the muscle and peritoneum together. If this is done it is not necessary to put separate stitches in the muscle but to make a good approximation, preferably overlapping the external sheaths of the recti. Tension sutures of nonabsorbable suture material are probably not necessary in the majority of cases, but I think it is wise to put three or four in every abdominal wound.

If patients are extremely obese with a large apron of fat in the abdominal wall, I have found it helps materially to make a large

transverse incision, excise considerable skin and subcutaneous tissue and then make the incision through the muscle in the median line. In this manner an abdominal retractor can be well placed in the muscle and the pelvis can be easily exposed (Fig. 4).

Many surgeons have been unfortunate enough to find an apparently aseptic wound without any sign of healing perhaps a week or more after operation, and when the superficial stitches are removed the edges of the skin separate and a loop of bowel presents itself. Such

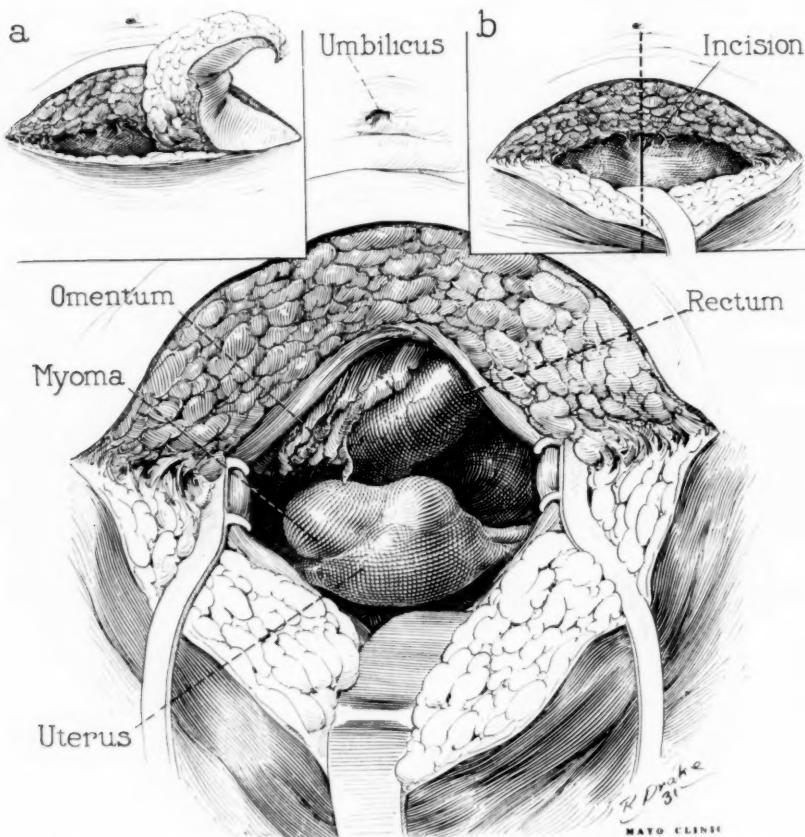


Fig. 4.—Lipectomy by means of transverse incision and median incision between the recti muscles and abdominal retractor on muscle edge.

hernias are caused, as Freeman suggested, by a piece of omentum that had been left protruding through the closure of the peritoneum when the wound was closed. It becomes swollen and edematous and a certain amount of fluid collects around it which flows along the wound, separating the approximated edges and preventing union. In other cases I believe union is delayed or prevented by a hematoma extending the entire length of the wound; when the catgut is absorbed the intraabdominal pressure is probably sufficient to open the entire

wound, especially if increased by complications such as distention, vomiting, use of stomach tube, coughing, hiccoughing, attacks of sneezing, or difficulty in defecation or urination. It cannot be a question of poor healing, as some patients are in good general condition, and secondary closure heals perfectly in the usual length of time. There is no doubt in my mind that many hernias which are not discovered until months after an operation begin in the same manner; in such cases only a small hernia develops and the remainder of the wound heals normally.

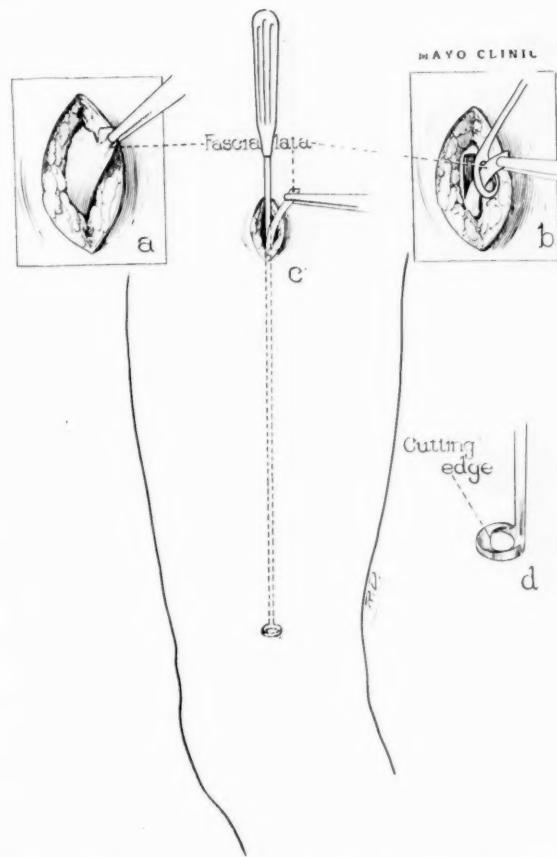


Fig. 5.—Method of obtaining living sutures from the fascia lata through a small incision.

If the hernia is small and situated about halfway between the umbilicus and the pubis, as a rule it will be possible to close the sac by much the same procedure as for an inguinal hernia. The fundus of the sac can be excised, the edges of the muscle thoroughly cleansed and brought together with mattress stitches of chromic catgut, and then an overlapping closure of the external sheath of the rectus can be made, also with the use of chromic catgut. If the opening is close

to the umbilicus, this type of closure will not be satisfactory as the recti muscles are likely to be widely separated and an overlapping closure is advisable. If the opening is small, it is best to make the closure from above down, but in most cases side-to-side overlapping is necessary.

If the opening is close to the pubis another difficulty is encountered, owing to the fixation of the recti muscles to the pubis, and if the hernia is the result of previous infection there is frequently considerable loss of muscular tissue. Freeing the rectus and pyramidalis muscles from the pubis on one side and approximating them to the other side has been advised, but I believe this is a dangerous procedure as it may be

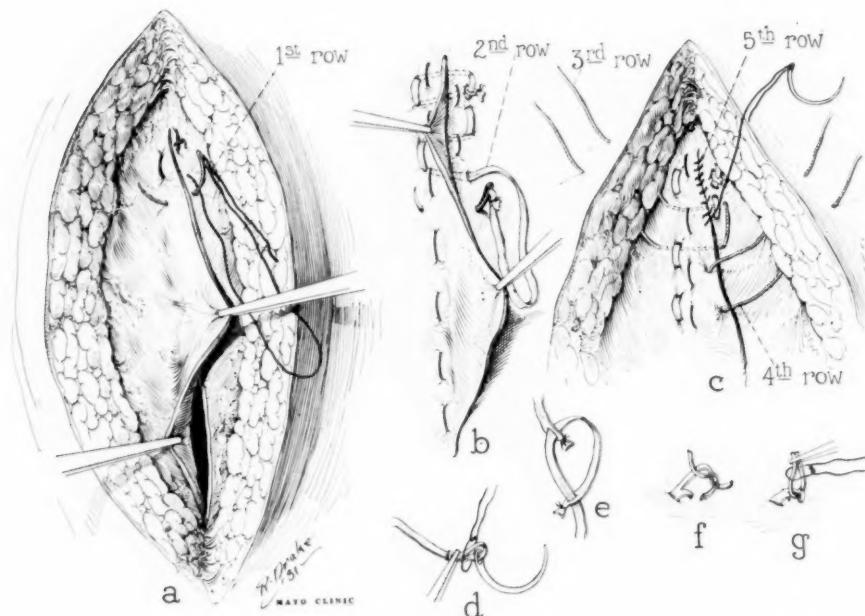


Fig. 6.—Closure of large hernias, a combination of plastic overlapping sutures and living sutures.

difficult to hold the cut end of the rectus down to the pubis and a weak wound may result. The procedure I have used for several years in such cases is to close such an opening with "living sutures" taken from the sheath of the rectus or from the fascia lata (Figs. 5 and 6).

In most cases the hernia extends throughout the length of the wound; in such cases I believe that the best results will be obtained by first thoroughly cleansing the sheath of the rectus of all areolar tissue, traumatizing or scarifying it on one side of the hernial opening for a distance of 2 to 2.5 cm., and excising the hernial sac; after separating any adhesions to the peritoneum for at least 2.5 cm. on each side of the wound, a plastic lateral overlapping closure of the Mayo type is used, bringing the cleansed peritoneum into accurate ap-

proximation to the cleansed scarified rectal sheath. If the separation is not excessive, such closure is satisfactory with the use of chromic catgut reinforced with several mattress stay sutures of silkworm-gut. In case the edges of the muscle are widely separated, however, such a closure is not satisfactory on account of the tension necessary to cause the edges to overlap; in such cases the use of several living sutures taken from the fascia lata as advised by Gallie is, to my mind, the greatest advance in hernial surgery in recent years. Strips of fascia can be obtained through a small incision in the upper part of the thigh by using the Mayo vein stripper to free them, and then a similar instrument with a cutting edge to free them at the lower end. I generally take a strip about 2 cm. wide and about 22 or 25 cm. long, and after removal cut it into three sutures each about 0.5 cm. wide. If more suture material is required, the process can be repeated, and in exceptional cases fascia can be taken from both thighs. The possible development of a muscle hernia in the thigh does not contraindicate the use of this method.

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**Reiprich: The Influence of the Male Sex Hormone on Female Sex Glands and Pregnancy.** Arch. f. Gynäk. 136: 417, 1929.

The author transplanted testes from male dogs into 25 females and from male white mice into females in an effort to produce changes in the female generative sex organs and also in an attempt to terminate pregnancy in those females which were pregnant at the time of the experiments. He was able to produce a very definite hormonal sterilization and also to interrupt pregnancy if the latter was less than one half way toward full term. In those few cases in which sterilization did not result, the subsequent litters were reduced in numbers. There was no apparent effect upon the sex of the offspring. The author describes in detail the pathologic and anatomic changes resulting from his experiments. These consist chiefly in an ovarian atrophy with atresia of the ovarian follicles. He was unable to obtain similar results in any of his control experiments, or by the use of various commercial testicular extracts. The gonads apparently have an antagonistic action for each other.

RALPH A. REIS.

## THE LENGTH OF LABOR\*

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**I**N THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY for February, 1930, there appeared an article on variation in the length of labor, in which a clinical analysis of 1,250 labors was made (Calkins). This published study was undertaken to determine what clinical factors had a bearing on the length of labor. Age and parity of the mother, as well as her height and weight, were studied. The height and weight of the child, the length of gestation, and the size of the mother's pelvis, as demonstrated by the length of the conjugata vera, were also included in the analysis. It was shown that, of all these clinical entities, parity alone had a bearing on the length of labor. Age of the mother, including the elderly primipara, was not found significant. Neither was the mother's height and weight important, thus contradicting the general belief that the fat woman is predisposed to a long, hard labor. The small pelvis, down to a size of 9.5 em. for the conjugata vera, was not found to cause a prolongation of the labor. Large babies, up to ten and one-half pounds, did not produce a marked prolongation of parturition.

Parity alone had a definite effect on the length of labor, there being a marked decrease in the length of both the first and second stages of labor in secundipara as compared to the primipara. There was, however, no marked change in the length of labors after the second, when compared to the length of the second labor.

Inasmuch as that study covered a series of only 1,250 patients and was, therefore, not entirely conclusive, it was considered advisable to analyze a larger series in a similar manner. The present study includes some 3,030 cases from the obstetric services of the University of Minnesota, some 1,450 consecutive labors from the University of Virginia and the University of Kansas, and 1,250 patients from the Henry Ford Hospital, making a total of over 5,700. This group has the added advantage of including a considerable number of private patients, as well as a wide variety of nationalities from various parts of the country, and three separate types of technics in the management of labor. It should, therefore, be a truly representative cross-section of the whole country and a series of 5,700 cases is sufficiently extensive to justify

\*Read at the Fifty-sixth Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 18-20, 1931.

rather definite conclusions as to the average length of labor and the various contributory clinical factors.

The simplest method of analysis, the average, was employed in this study. No other measure of variability or irregularity; such as within the range of distribution; will be included. The length of the first stage and the length of the second stage were analyzed separately. The effect of variation in age, in parity, in height of the mother, in weight of the mother, in length of gestation, in size of the pelvis, and in height and weight of the child, was determined with reference to each of the first two stages of labor. Occiput posterior presentation was contrasted with occiput anterior. No cases were excluded, save those where the clinical charts lacked the necessary data.

No attempt will be made in this presentation to compare our results with those of others recently published on various phases of this subject. Our method of analysis differs considerably but our conclusions are essentially in accord with the more recent articles.

#### AGE OF THE MOTHER

The primiparae were arranged in age groups at three-year intervals. The fifteen-year-old group included all patients fourteen, fifteen, and sixteen years of age; the eighteen-year group, those seventeen, eighteen, and nineteen years of age, while the forty-five-year group included all patients forty-four, forty-five, and over. The average duration of the first stage of labor was then determined in each age group. Fig. 1 (a) shows the result of these determinations. One hundred and two in the fifteen-year-old group showed an average duration of the first stage of labor of 13.2 hours, two-tenths of an hour more than the average for all primiparae. Six hundred and thirty-four cases in the eighteen-year-old group showed an average of thirteen hours, the same as the general average for the whole group. The line connecting the average for the fifteen-year group and the average for the eighteen-year group and projected on through the averages for the older age groups proves to be essentially a straight (solid) horizontal line. There is, therefore, no tendency for either increase or decrease in the first stage of labor, as we pass from the younger to the older age groups. There was not a sufficient number of cases to justify projecting this particular line beyond the thirty-nine-year-old group.

Multiparae arranged in similar age groups and with averages plotted in a similar manner showed the same general result. Whereas the plotted (broken) line is slightly irregular, there is no tendency for the average either to rise or to fall as one passes from the younger to the older groups of women.

Fig. 1 (b) shows a similar treatment for the second stage of labor. Multiparae present the same picture (broken line) as in the first stage. There is no tendency toward decrease or increase as one passes from the younger groups to the older. With the primiparae, on the other

hand, there seems to be a definite tendency toward an increase (solid line) in the length of the second stage as age increases. Primiparae of fifteen (87 cases) have a second stage twenty-eight minutes shorter than primiparae of thirty-three (61 cases) with the line of central tendency almost straight between these two average points.

It would seem safe to conclude that, whereas age has no effect on the length of the first stage of labor in either primiparae or multiparae nor on the length of the second stage of labor in multiparae, increasing age does slightly prolong the second stage of labor in primiparae. This effect is, at the most, a matter of a few minutes. Primiparae of fifteen have a second stage approximately ten minutes shorter than the

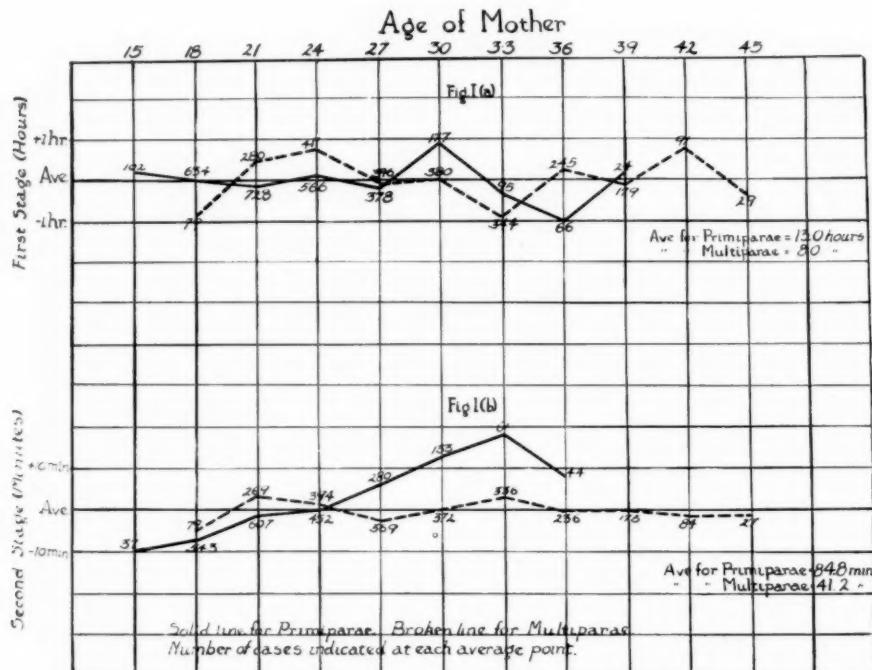


Fig. 1.

general average and primiparae of thirty-three have a second stage approximately seventeen minutes longer than the average. Contradictory to the generally accepted belief that elderly primiparae have long labors, it would seem reasonable to conclude from these figures that age has no considerable effect on either the first or second stage of labor, whether the patient be a primipara or a multipara.

#### PARITY

Fig. 2 (a) and Fig. 2 (b) are self-explanatory. In 2,791 primiparae there was a first stage average of 13 hours; 1,032 secundiparae had an average first stage of 8.2 hours, while 513 tertiparae had an average

of 7.3 hours. From the third labor onward there seemed to be a tendency toward a slight rise. Fifty-nine patients having their eighth labor showed an average of 9.1 hours for the first stage. Whether this increase is significant, as applied to the individual patient, is doubtful. The presence of scars or infection and hypertrophy in the cervix is probably more important than exact parity above three.

Fig. 2 (b) shows the duration of the second stage of labor developed in a similar manner. Here, again, we find a marked decrease from the 2,541 primiparae to the 1,003 secundiparae, amounting to thirty-three minutes. From the second labor onward, there seemed to be a slight

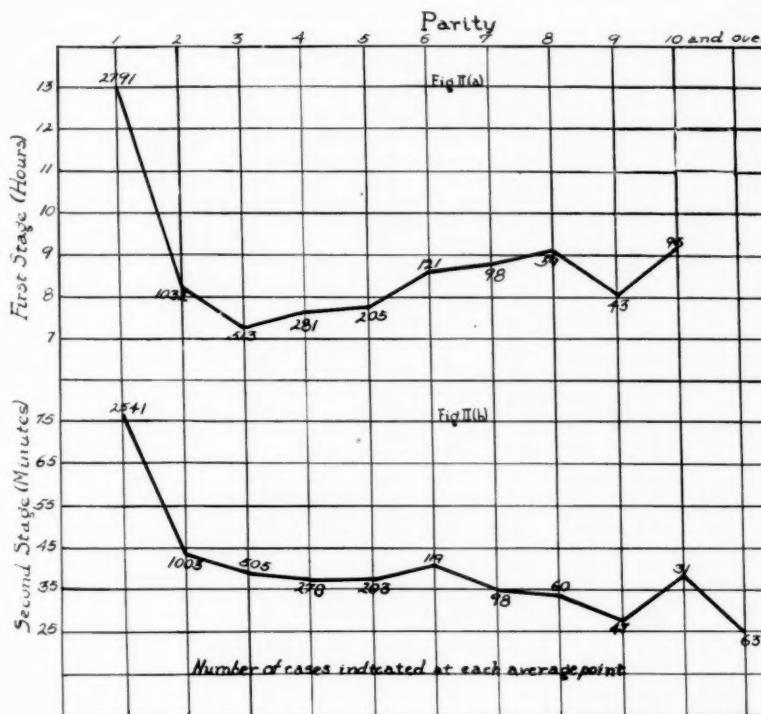


Fig. 2.

tendency toward decrease in each succeeding labor. However, the amount of this decrease would not be significant when applied to the individual patient.

Parity, then, has a very definite effect on the duration of both the first and second stages of labor. This effect, from a practical point of view, as applied to the individual patient, would seem to be confined to a difference between first and second labors. A multipara has an average first stage slightly more than 60 per cent of that of a primipara and an average second stage slightly less than 60 per cent that of a primipara.

## HEIGHT AND WEIGHT OF THE MOTHER

Only a portion of the charts from the Minnesota Clinic and the Henry Ford Hospital showed records of height and weight of the mother, so that while considerable new data were available for this study, the additional information did not change the results obtained in the previous study and no further discussion will be attempted at this time. It is our present belief that neither height nor weight of the mother has any considerable influence on the length of labor. On account of the lack of a sufficient number of case records, we cannot definitely establish this as a fact at the present time.

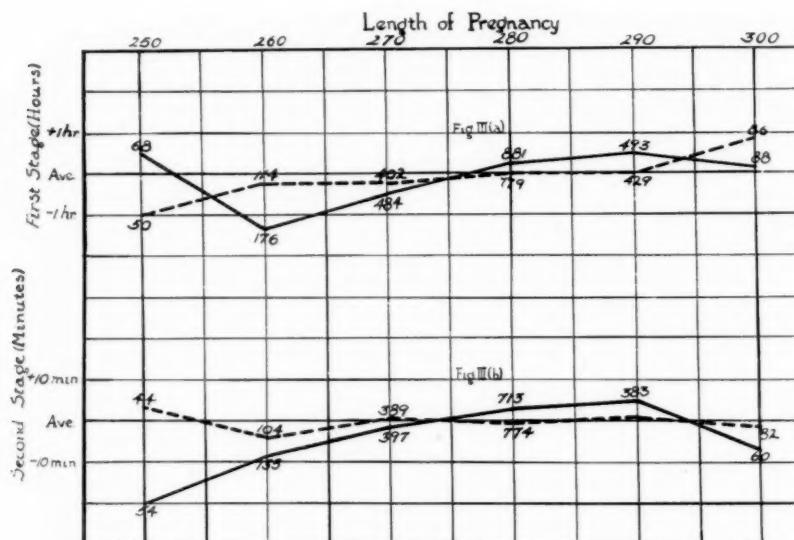


Fig. 3.

## SIZE OF THE PELVIS

From the previous study, it seemed quite evident that size of the pelvis, as represented by the length of the true conjugate, did not have any bearing on the length of labor. (This statement applies to a conjugata vera of 10 to 13 cm. inclusive.) The additional data available at the present time have not served to alter this conclusion.

## LENGTH OF THE PREGNANCY

The length of gestation, as measured by the menstrual history and divided into ten-day intervals from 250 to 300 days inclusive, when analyzed, produced the results shown in Fig. 3 (a) and Fig. 3 (b). In the multipara the length of pregnancy has no effect on the duration of labor. In the primipara it would seem that the longer pregnancies produce a very slight increase in both the first and second stages of labor. A pregnancy of 290 days required about an hour and a half

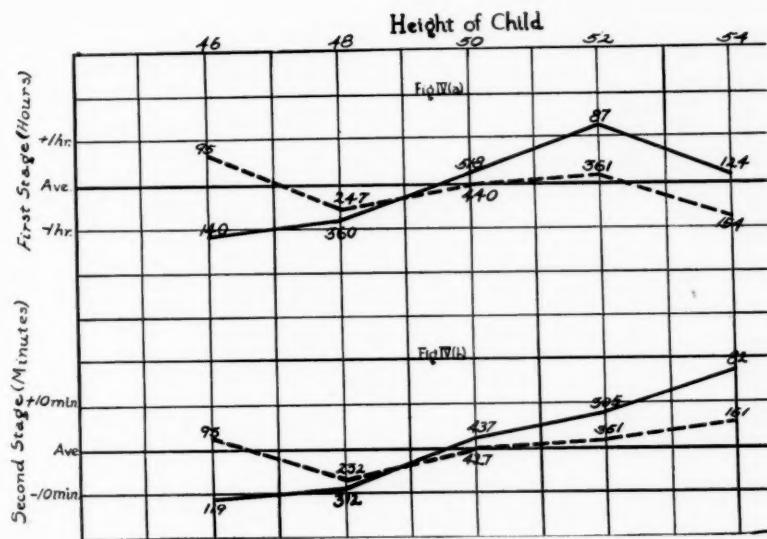


Fig. 4.

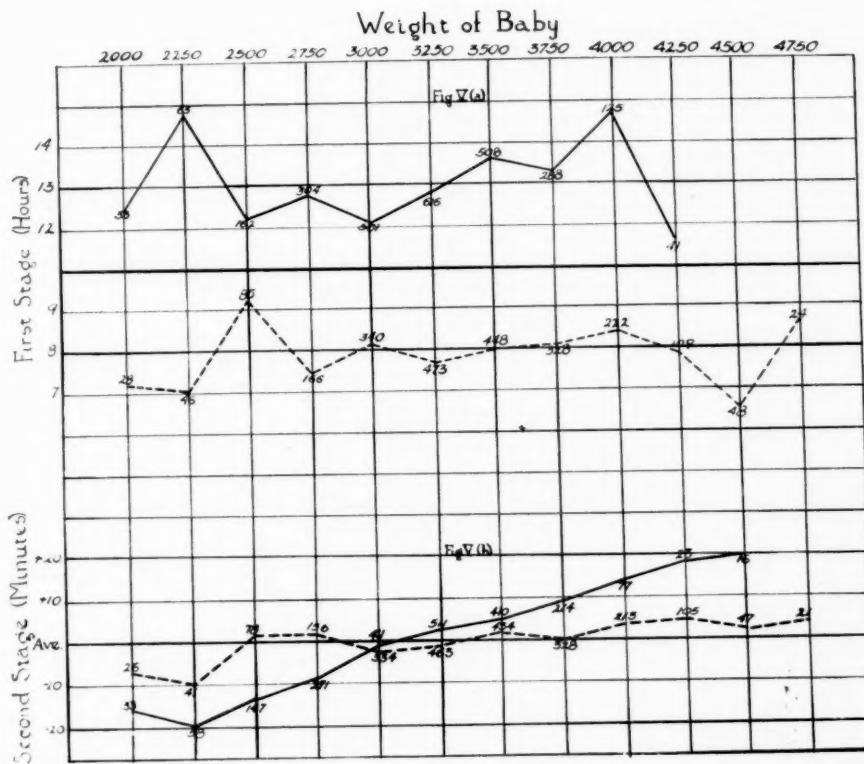


Fig. 5.

longer for complete dilatation than a pregnancy of 260 days. In the second stage, thirteen minutes more were required, on the average, for a pregnancy of 290 days than for one of 260 days. These differences are the result of averages in a large series of cases and are not of sufficient size to be of importance in the care of the individual patient. It is doubtful whether a study of the length of pregnancy for its effect upon the length of labor, can be considered very conclusive without a correction being applied for the coincident increase in size of the baby. As will be shown in the next section, the length of both the first and the second stages of labor in primiparae is increased proportionately with the size of the baby. This increase is more marked than that shown on Fig. 3. On this basis it might be concluded that length of pregnancy alone has no effect on the duration of either the first or the second stage of labor.

#### HEIGHT AND WEIGHT OF THE BABY

A study of the height of the baby (46 to 54 cm. inclusive) and weight of the baby (2000 to 4750 grams inclusive) revealed results as indicated in Figs. 4 and 5. For multiparae there is no increase in either the first or second stages of labor as one passes from small to large babies. In primiparae there is a considerable tendency toward prolongation of both the first and second stages when the babies are large. There is a difference in the first stage of nearly two hours between 48 and 52 cm. babies and between 3000 and 4000 gram babies. In the second stage there is a difference of about seventeen minutes between 48 and 52 cm. babies, and about twenty-five minutes between 2500 and 4000 gram babies. These differences would seem to be sufficiently significant to be applied to the individual patient in making up our judgment as to the progress of the labor.

#### PRESENTATION AND POSITION

The influence of presentation upon the duration of labor is shown in Table I. Occiput anterior, occiput posterior, and breech presentations are included. There were not sufficient numbers of the other types of presentation to justify computing averages.

TABLE I

	FIRST STAGE (HR.)	SECOND STAGE (MIN.)
<i>Primiparae</i>		
Occiput anterior	12.4 (2017 cases)	83 (1706 cases)
Occiput posterior	14.9 ( 630 cases)	95 ( 437 cases)
Breech	13.1 ( 95 cases)	-----
<i>Multiparae</i>		
Occiput anterior	8.2 (1837 cases)	40 (1758 cases)
Occiput posterior	9.2 ( 466 cases)	44 ( 440 cases)
Breech	9.1 ( 99 cases)	-----

From Table I it is apparent that occiput posterior results in a somewhat longer labor than breech presentation. It causes an increase over

occiput anterior, in the first stage of about two and one-half hours in primiparae and one hour in multiparae. In the second stage, occiput posterior delays delivery by twelve minutes for primiparae and four minutes for multiparae. A more frequent reiteration of the fact that labor is longer in occiput posterior than in occiput anterior might well serve as a potent factor in increasing our equanimity in the management of this presentation.

#### DISCUSSION

To summarize, it would appear that no one of the clinical factors studied affects the length of either the first or the second stage of labor in multiparae, except presentation. Occiput posterior results in an increase of about one hour in the first stage and four minutes in the second stage in multiparae.

In primiparae, a number of factors seem to have some influence on the duration of the labor. The exact effect of these factors, singly and in combination, is shown in Tables II and III.

TABLE II. LENGTH OF THE FIRST STAGE IN PRIMIPARAe

GENERAL AVERAGE IN 2769 CASES	15.0 HOURS	
<i>Increased by</i>		
Large baby (3750 grams and over)	503 cases	15.3 hours
Occiput posterior	702 cases	16.9 hours
Large baby and occiput posterior	138 cases	18.6 hours
<i>Decreased by</i>		
Small baby (2000 to 2750 grams)	610 cases	14.7 hours
Occiput anterior	2082 cases	14.6 hours
Small baby and occiput posterior	446 cases	14.6 hours

TABLE III. LENGTH OF SECOND STAGE IN PRIMIPARAe

GENERAL AVERAGE IN 2394 CASES	109 MINUTES	
<i>Increased by</i>		
Elderly mother (30 years and over)	295 cases	118 minutes
Occiput posterior	512 cases	119 minutes
Large baby (3750 grams and over)	410 cases	120 minutes
Occiput posterior and large baby	99 cases	149 minutes
Occiput posterior and elderly mother	43 cases	149 minutes
Large baby and elderly mother	37 cases	154 minutes
Occiput posterior, large baby, and elderly mother	10 cases	178 minutes
<i>Decreased by</i>		
Occiput anterior	1895 cases	107 minutes
Young mother (19 and under)	701 cases	102 minutes
Small baby (2000 to 2750 grams)	549 cases	98 minutes
Occiput anterior and young mother	482 cases	97 minutes
Small baby and young mother	156 cases	94 minutes
Occiput anterior and small baby	413 cases	92 minutes
Occiput anterior, small baby, and young mother	126 cases	92 minutes

From these tables, the extreme variation in the averages of the first stage of labor is four hours. Occiput anterior and a small baby has an average duration of 14.6 hours as compared to occiput posterior and a large baby where the average duration is 18.6 hours. The extreme variation in the averages for the second stage of labor is from 92

minutes for occiput anterior, small baby, and young mother, to 178 minutes for occiput posterior, large baby, and elderly mother. The gradations between these extreme averages for both the first and second stages in primiparae, are approximately what one would expect from the consideration of the various factors present in each group of cases.

The fact that of all the factors studied, presentation alone has a bearing on the duration of labor in multiparae and the fact that the various factors influencing the length of labor in primiparae have a comparatively small effect would seem to indicate that the most im-

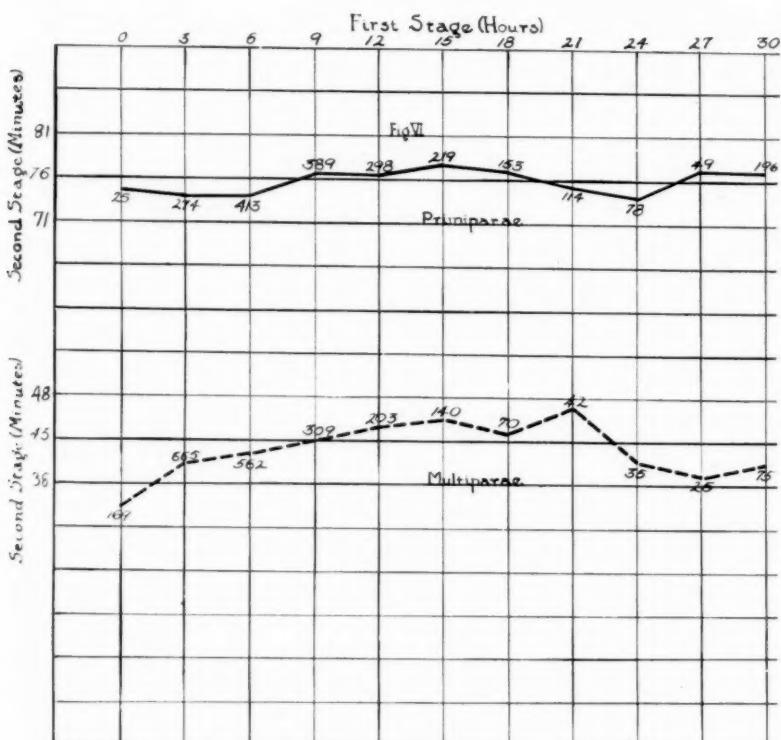


Fig. 6.

portant elements influencing the length of labor have not been included in this study.

It is generally believed that the relative (total) amount of amniotic fluid and the size of the bag of forewaters, as well as the time of its rupture, are matters of some importance in determining the length of labor. Close observation of a long series of cases would seem to indicate that this belief is sound; yet it does not seem that the membranes play any considerable rôle when applied to the whole group. One will encounter patients whose labors proceed quite rapidly following premature rupture of the membranes. Perhaps more often, one will encounter those whose labors are apparently prolonged on that account.

The resistance of the soft parts, particularly the cervix, is, beyond question, a factor of great importance in determining the length of the first stage of labor. The resistance of the pelvic floor, and occasionally of the vaginal walls in the primiparae, is also a factor of importance in determining the length of the second stage. Frequency, duration, and intensity of the uterine contractions are perhaps more important than any other factors in determining the length of labor.

A comparison of the duration of the first stage with the duration of the second (Fig. 6) reveals the interesting fact that in primiparae there is no connection between the duration of the first stage and that of the second stage. Two hundred and seventy-four patients with a first stage of from two to four hours had the same average duration for the second stage (seventy-three minutes) as that of 78 patients whose first stage was from twenty-three to twenty-five hours. In multiparae there seems to be a slight relation between the length of the first stage and the length of the second stage. Six hundred and sixty-five multiparae with a first stage of two to four hours had an average second stage of thirty-eight minutes, whereas 140 with a first stage of fourteen to sixteen hours had an average second stage of forty-eight minutes. Might we infer: 1. That in multiparae the labor pain is the most important item in determining the duration of the labor? 2. That in primiparae the resistance of the cervix and of the pelvic floor, along with presentation, size of the baby, and the age of the mother, is of almost equal importance with the character of the labor pains in determining the duration of labor? Clinical observation affords considerable evidence in favor of these inferences. Scar tissue, or infection and hypertrophy, in the cervix of the multipara retards dilatation a very little, in the presence of strong pains. A rather firm and resistant cervix in the primipara, on the other hand, materially delays the progress of labor, even though the labor pains be strong. Resistance of the pelvic floor is a much more important item in the primipara than in the multipara. Considering the labor pains alone, without regard to the resistances present, one frequently sees quite marked variations between first stage pains and second stage pains. This is particularly true in primiparae. Not infrequently, poor and ineffective first stage pains are succeeded by weaker contractions at or about the time the head reaches the pelvic floor, accounting for a large fraction of our low forceps deliveries. This may be due to a resistant pelvic floor in a patient whose cervix has dilated readily, but more commonly it is due to an actual weakening of the labor pains.

From Fig. 6 it is quite evident that in multiparae, accurate diagnosis and judgment of the progress of the first stage of labor will allow us to predict the probable duration of the second stage. In primiparae, on the other hand, the length of the second stage bears no relationship

to the length of the first stage. We must, therefore, reexamine our patient after complete dilatation and reconsider the forces and resistances involved before we can prognosticate the probable duration of the second stage.

#### SUMMARY AND CONCLUSIONS

From these inferences and the foregoing facts, it would seem that a more accurate observation of the *resistance* of the cervix (and the pelvic floor), as well as a more accurate determination of the *effectiveness* of the labor pains, will be necessary in order to analyze the causes for the extreme variations in the length of labor so commonly encountered. More accurate determination of the resistance would likewise enable us to predetermine the probable duration of the labor. Deliberate appraisal of the various factors present in any given labor, when balanced against a more definite knowledge of the *forces present and functioning*, might also serve to reduce our present high rate of operative interference.

To this end, it is suggested that the *consistency of the cervix*, as well as the thickness of its wall and the length of its canal, be *accurately determined and recorded* before labor begins or as early in labor as possible. Such a record on a scale of five (one being a very soft cervix, three, one of average softness, and five, a firm resistant cervix) has been kept on a few hundred cases with surprisingly satisfactory results. It is suggested that the *effectiveness of labor pains* be more accurately *determined and recorded* for the purpose of increasing our ability to determine the probable length of labor in each given case. Experience with a small series thus estimated on a scale of five (with one and two representing poor pains, three average pains, four hard pains, and five abnormally hard pains), has proved very suggestive. In the grading of labor pains, more attention is paid to the intensity of the contraction than to duration or frequency, although all three factors must be given consideration. Intensity of first stage contractions can be satisfactorily estimated by digital (not palmar) palpation of the fundus or by palpation of the tension, and amount of stretching, produced in the cervix. It is believed that digital palpation of the fundus (not the lower uterine segment) is more accurate than palpation of the cervix. Likewise, in the second stage, digital palpation of the fundus is preferred to the determination of the amount of descent or the amount of stretching of the pelvic floor.

It is believed that accurate determination of the effectiveness of the labor pain balanced against the resistance of the cervix and pelvic floor, is the all-important factor in determining the length of labor. The other variants, as analyzed in this study, are of only minor importance.

## THE TREATMENT OF THE VERTEX OCCIPITO- POSTERIOR POSITION\*

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**I**N PRESENTING another paper concerning the much-discussed vertex occipitoposterior position I am prompted by the realization that this complication still causes those who practice obstetrics more trouble than any other. By this, of course, I do not mean that it is the most serious complication, but because of the frequency of its occurrence, it is a very common source of annoyance. Numerous articles in the recent literature do not indicate that the problem of managing labors complicated by this abnormality has reached a solution at all satisfactory. I have never considered the occipitoposterior as a complication difficult to overcome and, therefore, my thoughts are directed toward the real cause of difficulty. Is the fact that the posterior position continues to be a serious problem, due to unsatisfactory methods of delivery with a lack of standardization or is it due to an unsound policy as to the question of interference on the one hand and watchful waiting on the other? Probably both factors are to blame. As important as is the proper selection of methods of delivery, perhaps of equal importance is the determination of the proper time during labor at which delivery should be accomplished. It seems to me that the teaching of the management of this complication is most confusing to the practitioner both as regards the general policy and in respect to the delivery methods used. There are two methods of procedure which are perhaps equally faulty. One is that of too early interference, that is in the first stage of labor, and the other is that of too long waiting for spontaneous rotation after full dilatation of the os has been accomplished. I would suggest a modification of the general teaching that the waiting policy is the safer one and urge that this policy apply only to the first stage of labor. In my opinion the general teaching that in most of these cases the head will rotate spontaneously and that therefore the treatment should be expectant, has been one of the greatest factors in the continuance of a too high fetal mortality rate. The teaching, that the place at which the head should normally rotate is on the pelvie floor, has also been responsible for too great delay in interference and consequently unsatisfactory results. In many cases the head will reach the pelvie floor only after an inexcusably prolonged second stage of labor which has worked to the detriment of both

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mother and child and in other cases the head will not reach the pelvic floor at all, while in the posterior position. The idea that the pelvic floor is the proper place for rotation has also led to the faulty method sometimes advocated of drawing the head down to the pelvic floor with forceps and then rotating. The traction force necessary to bring a fetal head down to the pelvic floor while in a posterior position is so far in excess of that required to accomplish the same thing when the occiput is anterior, that it can never be considered justifiable.

I look upon the persistent posterior position as a distinct abnormality which should be treated as such by proper interference early in the second stage of labor. To expect the forces of the uterus and abdominal muscles directed toward the pelvis and in a line with the child's body, to produce a rotary movement of the fetal head sufficient to turn it 135 degrees is scientifically unsound. Much of the force so expended is wasted, the result being unnecessary fatigue of the mother and harmful pressure on the child's head. Statistics all show that fetal mortality rises as the length of second stage labor increases.

Ideal results must not be judged by the fact of eventual spontaneous rotation of the head but by the condition of the child at birth and the conservation of the mother's strength. Furthermore, in those cases in which the posterior position is persistent and interference is eventually resorted to, the delivery may be very much more difficult because of the undue prolongation of the second stage. Many very difficult deliveries would have been easier deliveries if earlier interference had been the policy. For example, if the head remains high and the elective procedure is delivery by podalic version the ideal time to perform the version is while the contractile activity of the uterus is such that it will relax under an anesthetic and before there is developed a tonic state of contraction, or even a contraction ring. Too long delay sometimes makes the performance of this elective procedure impossible and necessitates the use of either the more dangerous high forceps or even the performance of a cesarean section. In my opinion cesarean section needs seldom if ever be performed because of the occiputoposterior position. In the series of cases which I shall report none of the cesarean sections included in the list were performed because of the posterior position but because of a contracted pelvis, the diagnosis of the occiputoposterior position being merely incidental to the case. Practically the only indication for cesarean section referable to the posterior position is that of dystocia due to the cervix, which is more common in posterior positions than in anterior positions. The example of this is the occasional case in which with very little dilatation the fetal heart shows signs of irregularity and calls for interference of some kind.

The policy which I have followed throughout my entire practice and which I advocate to trained obstetricians may seem radical but I

personally have become more and more convinced of its soundness with each succeeding year of practice. In this connection I should like to make it perfectly clear that this policy is recommended for those trained in obstetrics and is not a compromise of ideals to suit the methods which are within the resources of physicians unfamiliar with obstetric procedures and without the background sufficient to supply the judgment essential for proper application of methods. I fear that such a compromise of ideals has to a considerable extent retarded the adoption of successful procedures and unfavorably modified the teaching of obstetrics. This comment would apply, however, to more phases of obstetrics than the occipitoposterior position. The methods which I advocate in this paper are, however, those which are taught to our residents in training and satisfactorily carried out by them. The experience, therefore, which I and my associates at the Cleveland Maternity Hospital have had in the treatment of occipitoposterior positions is such as to amply justify our satisfaction with the methods used. The policy is that of extreme conservatism and watchful waiting in the first stage of labor combined with one of active interference at the beginning of the second stage. In the first stage of labor noninterference is the watchword and with this is intimately bound the relief of pain. The first stage is ordinarily somewhat prolonged, sometimes very markedly so, and therefore where methods for the relief of pain have not been used, the prolonged suffering of the patient has in many cases induced the physician to interfere before the complete dilatation of the cervix. In my opinion attempts at delivery before the termination of the first stage of labor have resulted in higher fetal mortality than that due to contraction of the bony pelvis. Where pains of labor are relieved and sufficient time allowed, spontaneous dilatation of the os will ordinarily result. Manual dilatation of the os should be used only in cases of emergency usually due to a failing fetal heart. The necessity of such a procedure, however, is not often seen.

Inasmuch as the satisfactory conduct of the first stage of labor depends to a large extent upon the relief of pain, I shall mention briefly the common methods which we use for this purpose. In primiparae morphine and scopolamine analgesia is used to a stage three hours before the expected birth of the child. When pains become harder this is supplemented for complete relief, by inhalation analgesia, gradually increasing to anesthesia. In some cases colonic ether is given between the scopolamine stage and that of anesthesia. This variation depends somewhat upon the length of the first stage. In cases of multiparae, sodium amyta is the routine administration followed by either colonic ether and then anesthesia or by inhalation analgesia and anesthesia. The general anesthetics used for delivery are ether, and nitrous oxide and oxygen. The choice between the two depends largely upon whether

one desires complete relaxation of the uterus as in the case of a version; or, prefers less relaxation as in the case of a forceps delivery. A certain amount of dilatation of the os is not deemed essential as an index of the time to start analgesia. The fact that the patient has pains which hurt her is sufficient regardless of dilatation.

In the dry labor with the fetal head high and in the posterior position, progress is occasionally so slow that there is a real danger of fetal distress before sufficient dilatation may be accomplished. In some of these cases it is better to insert a bag and promote more progressive dilatation, though this is by no means a common necessity. As mentioned before, an occasional case of this type may require cesarean section. In the series of cases reported in this paper, cesarean section was not performed for this reason though in one case it probably should have been.

While the first stage of labor may be considered one of watchful waiting and the relief of pain, that is, nature's stage, the management of the second stage of labor is surely the physician's problem and the labor has then reached a point when with proper delivery methods used early he may obtain uniformly good results. I believe that by careful observation an obstetrician should be able to determine very early in the second stage whether spontaneous rotation will occur promptly, or whether if at all only after many additional hours of labor. It seems to me that one hour of second stage labor should be sufficient for such a test. Personally I do not wait at all for spontaneous rotation after the os has become fully dilated. The common belief that in a primipara the fetal head should be engaged at least two weeks before the onset of labor needs considerable modification in the cases of posterior positions. In a very considerable percentage of these cases the fetal head is unengaged at the time of the onset of labor and still remains unengaged at the beginning of the second stage. It is impossible to make these heads fit into the pelvic brim by pressure and were it not for the diagnosis of a posterior position there might be a decision to perform a cesarean section. However, in such a case the head when rotated to an anterior position or when delivered as an after-coming head, after podalic version, may be made to pass through the pelvic brim with ease. Undoubtedly a good many cesarean sections are performed in cases of this type when the fact of the high head is not due to the pelvic dystocia but is due merely to the faulty position. To expect the fetal head to be forced through the pelvic brim in such an unnatural position by the prolonged action of the forces of labor; by stimulation of the uterine muscle by drugs; or by the application of an extremely tight abdominal binder; or to pull the head through the pelvic inlet with forceps while in a posterior position, would seem to be the height of folly. After full dilatation the faulty

position should be corrected without further delay. The patient may be saved further labor and the baby delivered with uniformly good results by the proper procedures.

My selection of methods for delivery in vertex occipitoposterior position was influenced to a large extent by two things. First, a decision not to use the high forceps operation except in extreme emergencies; and, second, never to deliver the head in the posterior position, nor to make any traction upon a head while still in the posterior position with the idea of bringing it down to a lower pelvic plane. Thus, when a decision to deliver a patient is made, the abnormality of position is corrected first of all and before any attempt at delivery is made.

I have reduced the procedures used to two; internal podalic version, followed by immediate extraction; and, rotation of the head by forceps according to what has been termed the "modified Seanzoni" maneuver, followed by forceps extraction. Following the principle of the disuse of the high forceps operation, whenever the largest diameter of the fetal head has not passed through the pelvic inlet, internal podalic version is performed as the procedure of choice. When the largest diameter of the fetal head has passed through the pelvic inlet and the head is in the pelvic cavity, forceps delivery is performed. I personally never attempt manual rotation of the head nor rotation of the body of the child by intrauterine manipulation. It seems to me that the intrauterine manipulation necessary to accomplish this is as great as the manipulation necessary to perform a version and after it is accomplished one still has the problem of the delivery of the child to face. When the head is in the pelvic cavity and manual rotation is attempted, the head is commonly displaced to a considerably higher level so that after the rotation one has to deal with a high head instead of one which is well down in the pelvis. The head is also undoubtedly more likely to rotate back to the posterior position after manual rotation than after forceps rotation.

When forceps rotation of the head is performed the head remains practically in the same pelvic plane throughout the rotation and descends to a certain extent immediately upon completion of the rotation, being then in a lower pelvic plane for the subsequent delivery.

Some question has been raised as to just what the "modified Seanzoni maneuver" is. I personally have claimed very little credit for this procedure as an original operation. However, as slight as the modification may seem to be, it is to my mind, of the utmost importance for the success of the maneuver. The only element of modification of this procedure which I have stressed is that while rotating the head, instead of performing rotation and traction at the same time, producing thereby a spiral movement of the head and causing descent during rotation, the head is rotated in the pelvic plane in which it lies with no traction whatever. The misleading statement has been

made that I push the head up before rotating. I never deliberately do this but have said that sometimes during rotation if the head seems to be too well fixed in the pelvis, a very slight upward pressure may facilitate the rotation. Usually even this is not done. The following are the important steps in the technic of the forceps delivery of the occipitoposterior position, each one of which is important for the success of the procedure:

First: There should be complete dilation of the os.

Second: The fetal head should be in the pelvic cavity.

Third: The membranes should be ruptured or are artificially ruptured before the application of the forceps.

Fourth: Thorough manual dilation of the whole birth canal below the head is performed so as to eliminate as far as possible resistance to the head in the course of the subsequent delivery. This, however, has nothing to do with the rotation. Episiotomy is performed only in cases of unusual rigidity in which sufficient dilatation cannot be accomplished by the ironing out process; or, in cases in which due to a failing fetal heart, it is wise to eliminate all possible resistance and hasten the birth.

Fifth: A cephalic application of the forceps is made with the concavity of the blades looking forward; that is, toward the baby's face.

Sixth: Before locking the forceps the handles are depressed somewhat so as to bring the blades of the forceps more nearly in the long diameter of the ovoid which has as its poles the vertex and the chin. This is advisable inasmuch as there is, as a rule, in these cases poor flexion of the head.

Seventh: The forceps are locked and the handles are raised toward the opposite groin of the patient. This maneuver has a tendency to favor flexion of the head.

Eighth: Without any traction the handles are then carried around in a large circle so that during the various stages of rotation they point first toward the groin of the patient; next, toward the thigh; and, next almost downward toward the floor. With this sweep of the handles the blades of the forceps do not deviate from the same axis during the process of rotation and the fetal head turns with them with the use of very little force on the part of the operator.

Ninth: The rotation is continued until the occiput lies directly under the symphysis pubis and the sagittal suture is in the anteroposterior diameter of the pelvis. The extent of this rotation is important in preventing a return of the head to its original position after the forceps are removed. When the head is rotated merely to the oblique diameter there is greater likelihood of its becoming posterior again when the forceps are removed.

Tenth: Before the forceps are removed some traction is made, with no idea of delivering the head, but simply enough to fix it in its new position. If the patient is under complete anesthesia at this time, the anesthetic is now taken off so as to favor uterine contractions which tend to further fix the head in this position, before the forceps are removed. The forceps are then removed and re-applied as to any normal anterior position.

Eleventh: In the reapplication of the forceps there are certain points which are important to observe and which have to do with the prevention of the return of the head to a posterior position, an experience which has bothered many who have tried this procedure. These are:

a. The posterior blade should always be applied first. For example if the case has been one of right occipitoposterior the right blade is put on first. After this blade is inserted there is little or no chance of the head turning back during the application of the anterior blade.

b. The posterior blade should be inserted with as little manipulation as possible. If before inserting this first blade, the physician is too intent upon digital examination of the sutures and fontanelles and in doing so pushes the head upward it will very likely slip back into its old position. But if the blade is applied promptly and with little or no disturbance of the head this will not occur. After the blades are applied to the head in its new anterior position a check should be made to see that the most perfect cephalic application is had. The best test of this is that the anterior edges of the blades should lie parallel to and equidistant from the lambdoid sutures. If this condition is present, one always has an ideal cephalic application.

Twelfth: Traction is then made coincident with the contractions of the uterus so as to diminish as far as possible the necessity of traction force. An axis traction appliance is always used because it is thought that the increased accuracy in the direction of traction thus obtained, tends to further diminish the force required, in other words, to eliminate wasted force. When the head is brought down to where it is well fixed in the vulvar orifice, the forceps are removed and the head is shelled out manually. The rotation of the head is accomplished more easily with a forceps having a pelvic curve. There is no need of a straight forceps. I use the Tucker-McLane solid blade forceps with axis traction appliance and believe that it is by far the most satisfactory instrument for this work.

This entire procedure contrary to frequent statements is a thoroughly safe and invariably successful procedure. It is a gentle manipulation in no part of which is any amount of force used, and when carried out according to the technic described offers practically no danger of injuring either the mother or the baby. To my mind it is far superior to any other forceps operation for the delivery of the occipitoposterior head which has ever been suggested. It is a thoroughly scientific procedure in that it first of all corrects the abnormality of position and nothing more, and leaves the delivery to be treated as that of a perfectly normal anterior position. If the head is in a position of partial rotation, that is, of transverse arrest, one application of the forceps is sufficient. This also should be a cephalic application by which rotation is completed.

When the head remains high and the largest diameter has not passed through the pelvic brim, internal podalic version is probably the more satisfactory procedure, not that rotation cannot be accomplished perfectly well by the forceps when the head is high but that the subsequent delivery after rotation would be that of a high forceps. If after full dilatation of the os the head is still high and in a posterior position and the membranes are intact, the method of rupturing the membranes and waiting for spontaneous rotation is not without danger for if rotation and descent do not occur, and version is then deemed the operation of choice, it is naturally a more difficult procedure. Inasmuch as in my practice podalic version is the procedure of choice under such conditions and inasmuch as we know that podalic version is more easily performed before the membranes have ruptured, I follow the principle of performing the delivery promptly and while ideal conditions

exist. Such a version is in reality a prophylactic version. If the membranes have already ruptured and at the time of the full dilation of the os the head is still high, the more promptly the version is performed the more certain will one be of a successful termination of labor.

The technic of internal podalic version and breech extraction has been so thoroughly described by Irving Potter that further comment would seem unnecessary. I should like to point out, however, those steps in the procedure which seem to be the most essential for a smooth delivery and satisfactory result. These are:

- First: A thorough dilatation of the entire birth canal.
- Second: Use a relaxing anesthetic so that there will be no tendency for the uterus to contract during the course of the version.
- Third: Use a long rubber glove.
- Fourth: If the membranes are intact, retain all fluid possible by rupturing them, near the location of the feet.
- Fifth: Attempt to determine the location of the cord and prevent if possible the occurrence, during the subsequent extraction, of a straddled cord which might make considerable trouble.
- Sixth: Bring down both feet together with the heels to the front.
- Seventh: During the extraction of the buttocks make no attempt to keep the sacrum of the child toward the front for it invariably turns into a sacroposterior position during its descent through the pelvis.
- Eighth: After the buttocks are delivered, favor anterior rotation so as to bring the back of the child to an anterior position.
- Ninth: Deliver the shoulders by a twisting and downward movement of the body which rotates the anterior shoulder under the pubic arch and tends to sweep the arm of the child toward the chest. Sometimes the entire arm will come out with this procedure and sometimes the arm will lie across the child's chest but still in the pelvic cavity from which point it may be easily picked out by one finger hooked in the bend of the elbow. The second arm is also brought out as an anterior arm by turning the child's body in the opposite direction and duplicating the former procedure.
- Tenth: If the head is still high, be sure that it does not lie in the antero-posterior diameter of the inlet. To attempt to deliver the head in this position might be disastrous. I therefore lay great stress upon the principle of always making sure that the child's head lies in the oblique diameter of the inlet before any attempt at delivery is made.
- Eleventh: Do not use the Mauriceau grasp on the child's shoulders but with the finger of the internal hand in the child's mouth, which serves more to aid flexion than anything else, deliver by pressure with the other hand above the symphysis and upon the child's head. I find it rarely necessary to use forceps upon the after-coming head.

As to the results which we have obtained at the Cleveland Maternity Hospital by following the general policy and methods of delivery which I have described I shall quote two groups of statistics. First, I would refer you to an article upon this subject appearing in the *Journal of the American Medical Association*, under date of May 9,

1931, by Samuel M. Dodek, at present Research Fellow in Obstetrics at Western Reserve University.

In this article, Dodek reports a series of cases of occipitoposterior position in which labor had been conducted and delivery accomplished by the Resident Staff. You will note that the Residents had a tendency to wait a little longer in some of these cases than is my own practice. However, the same general policy was followed and the same methods used. Of the cases allowed to remain in the second stage for longer than the usual time "only 26 per cent rotated spontaneously, and of these 5 were in the second stage over three hours; 5 for four hours; 4 for five hours or more; 3 for six hours; and one for seven hours." This will illustrate the futility of waiting in the second stage.

In this series there were 514 cases, in which the head rotated spontaneously in 148 cases. Fifty-nine were delivered by internal podalic version; 276 by the modified Seanzoni maneuver and 12 after manual rotation. There were 18 cesarean sections in this series but in these cases the posterior position did not furnish the indication for cesarean section. As to the details of this series I refer you to Dodek's paper, but merely note here that in the entire series the fetal mortality was 4.47 per cent for all babies, and that excepting fetal deaths due to conditions which had nothing to do with labor, such as prematurity, monsters macerated fetuses, etc., the corrected labor and delivery mortality for the child was 3.1 per cent.

In addition to this series I have analyzed the last 500 consecutive cases of vertex occipitoposterior positions which I personally delivered. In this series no cases of spontaneous rotation of the head are included, the head being in the posterior position in each case at the time of delivery.

There were 219 primiparae and 281 multiparae in this series, as follows:

Para	i	219 cases
	ii	161 cases
	iii	70 cases
	iv	31 cases
	v	12 cases
	vi	5 cases
	vii	1 case
	viii	1 case
	Total	500 cases

In all of these cases labor was conducted practically painlessly, the various methods used being as follows:

Morphine and scopolamine followed by ether, in	196 cases
Morphine and scopolamine followed by nitrous oxide	36 cases
*Ether analgesia and anesthesia, in	142 cases

\*Note: These cases were delivered before the use of sodium amytal was begun.

Nitrous oxide, analgesia and anesthesia, in	28 cases
Sodium amyta followed either by inhalation analgesia and anesthesia; or by colonic ether and later by general anesthesia, in	85 cases
Colonic ether followed by inhalation ether, in	13 cases
	—
Total	500 cases

The methods of delivery were as follows:

Modified Scanlon method, 172 cases:	High medium forceps	34 cases
	Low medium forceps	89 cases
	Low forceps	49 cases
	—	—
	Total	172 cases
Internal podalic version and breech extraction		317 cases
Abdominal cesarean section		11 cases

Manual dilatation in cases of emergency in which the os was not completely dilated, was performed in 11 cases.

The Voorhees bag was used 11 times.

Episiotomy was performed in 50 cases.

Forceps were not applied to the after-coming head in any of these cases.

In the entire series there were 10 fetal deaths, of which 7 babies were stillborn and three died during the first two weeks. Of the three which died subsequent to delivery, autopsy showed congenital anomalies of the heart in two and enlarged thymus in the other. The deaths were attributed to these conditions. Of the stillborn babies two were macerated having been dead before the onset of labor. Thus there were five fetal deaths which could in no way be attributed to the labor or delivery. The five stillbirths in which the cause of death could be attributed to the labor or to the delivery were as follows:

Asphyxia due to separation of the placenta	2 cases
Asphyxia due to unusually prolonged first stage of labor	2 cases
Birth injury (?)	1 case

In the two cases of separation of the placenta the accident occurred late in labor and with a failing fetal heart in each case. Version was performed but too late to save the baby. In the two cases of prolonged first stage of labor the fetal heart became very irregular in each before there was complete dilatation of the os. In one of these, podalic version was performed. In the other there was a tonic contraction of the uterus and contraction ring. The delivery was by forceps. This was a case of an elderly primipara with a very rigid cervix. Cesarean section undoubtedly should have been performed early in labor. The fifth case was apparently an easy one. The patient was a primipara. Labor was of normal duration, and the fetal heart was normal at the time of delivery. Delivery by version was not at all difficult. The cord was pulsating at the termination of the birth, but ceased almost immediately and all efforts at resuscitation failed. Fetal heartbeats were never heard during efforts at resuscitation. At autopsy only two things were found. There was a slight tear of the tentorium but no

accumulation of blood. The heart was about one-half normal size and the foramen ovale was large enough to admit the little finger. Otherwise the heart was normal. The death was attributed to the tear in the tentorium, although the diagnosis was somewhat in doubt.

There were therefore, in the 500 cases, 5 fetal deaths, which could be attributed to the labor or the delivery or 1 per cent fetal mortality.

In the 172 cases delivered by the modified Seanzoni method there was one fetal death or 0.58 fetal mortality.

I would attribute the slightly lower fetal mortality of my series as compared with that of the residents, if to anything except their unusually difficult cases, to the fact that I have been less inclined to wait for spontaneous rotation and as a rule have interfered earlier in the second stage.

Altogether our results show that when these methods of delivery are used at the most suitable time for delivery, which is early in the second stage of labor, uniformly good results may be expected.

OSBORN BUILDING.

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Hogben, L.: **The Scientific Basis of Organotherapy.** J. M. A. South Africa 3: 663, 1929.

Organotherapy is discussed from the standpoint of the experimental biologist. The importance of the appropriate methods of preparation, standardization, and administration of biologic products is stressed. It is pointed out that the medical profession is more apt to accept the interested testimony of the manufacturer, rather than to rely on laboratory investigations. The author believes that important contributions will ultimately be made by the study of the internal secretions, but at present if the clinician proceeds to make use of commercial preparations of doubtful activity, organotherapy will be brought into disrepute and research will be impeded rather than advanced. He states that endocrinology is at the moment the nucleus for some of the wildest, most undisciplined and discreditable speculations that can be extracted from contemporary science, and concludes that scientifically, "the glandular temperamentalists are in the same hierarchy as the palmists and astrologers."

FRANK SPIELMAN.

## PROGNOSIS IN NEPHRITIS COMPLICATING PREGNANCY\*

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**I**N 1926 we proposed a classification of the toxemias of pregnancy which included the groups designated as "low reserve kidney" and "chronic nephritis." We have made use of this classification since the above date and have found it generally satisfactory, provided the diagnosis in each case is made by following strictly the criteria suggested for its establishment. There are certain defects in the classification, particularly in connection with the differentiation between a severe "low reserve kidney" and a mild "chronic nephritis"; consequently, we will leave for a later paper the consideration of differential diagnosis between chronic nephritis and other types of toxemia of pregnancy.

During the past several years, we have been impressed with the number of women receiving care in our clinic who succumb to nephritis either while in the hospital or within a few years after discharge. For this reason we have attempted a complete as possible follow-up study on a fairly large series of patients suffering from nephritis, namely, 236 patients with 297 hospital admissions, who were admitted to our service during the ten-year period from January 1, 1919, to December 31, 1928. We have been able to obtain the full service of a social worker who visited the patients at their homes and brought them back to the clinic for reexaminations. In this manner, we have been able to trace over 57 per cent of the patients studied, and are in a position to draw final conclusions about 135 women in whom the diagnosis of nephritis complicating pregnancy had been made while in the hospital. The findings in these statistical and follow-up studies are presented in tables, supplemented by charts.

From Table I it will be seen that our patients were almost equally divided between whites and blacks. Of the total admissions, about half were delivered at full term, while premature termination of the pregnancy occurred in 17 per cent, and spontaneous or therapeutic abortion in 15 per cent. Of the 260 pregnancies observed on the service 63.46 per cent were allowed to go to term, 19.23 per cent terminated prematurely but after the child had reached a period of viability, while the remaining 17.31 per cent were abortions.

In Table II is given the age of the patients when the diagnosis of nephritis was made, as compared with that of the general clinic popu-

\*Read before the East New York Medical Society, December 22, 1930.

TABLE I. DATA ON ADMISSIONS OF NEPHRITIC PATIENTS  
JAN. 1, 1919 TO DEC. 31, 1928

Total patients		236	
Admitted twice	28	28	
Admitted three times	12	24	
Admitted four times	3	9	
Total admissions		297	
			PER CENT
Type of admission:			
Full-term spontaneous	97	97	55.55
Full-term operative	68	68	
Premature spontaneous	18	18	16.84
Premature operative	32	32	
Abortion spontaneous	17	17	5.72
Abortion therapeutic	28	28	9.43
Not pregnant	7	7	2.36
Postpartum	4	4	1.35
Discharged before delivery	26	26	8.75
	297		100.00
Race:			
White	115	or	48.73
Black	121	or	51.27

lation. It will be noted that nephritis is relatively much more common between the ages of thirty and forty years, while its incidence is low in the women below thirty years of age. This is strikingly illustrated when we note that about 90 per cent of the total number of patients admitted to the clinic were under thirty years of age, whereas only 46 per cent of the nephritic patients fall in that age group. The increased age of the nephritic woman is further demonstrated by the fact that her mean age, when first seen with nephritis was over six years greater than that for the general clinic population.

Studying the incidence of nephritis from the point of view of parity, we observe that it increases with multiparity. Although over 50 per cent of all the patients in our clinic during the ten-year period under consideration were primigravidae, only 30 per cent of our nephritic patients belong in that group. In Table III, we have compared the incidence of the nephritic patients with the total material of the clinic, and this shows that as the third pregnancy is approached the incidence of nephritis becomes and remains higher than the incidence of our total clinic material for the various parity groups. This is graphically demonstrated in Fig. V.

As will be seen from Table IV, only 4 per cent of our nephritic patients had previous eclampsia. This is a very low figure when we consider that about one-fifth of all eclamptic patients develop permanent kidney damage, and is, of course, dependent upon the fact that chronic nephritis occurs much more frequently in pregnancy than does eclampsia. From this table it will also be noted that less than 10 per cent of the nephritic patients had a definite complicating heart dis-

ease; an interesting observation in view of the opinion of some that cardiac involvement is a usual accompaniment of chronic nephritis.

TABLE II. AGE OF PATIENTS WHEN FIRST SEEN WITH NEPHRITIS

AGE	CASES	PER CENT	PER CENT OF PATIENTS IN EACH
			AGE GROUP IN ENTIRE HOSPITAL
- 19 years	27	11.44	43.8
20 - 24 years	43	18.22	32.1
25 - 29 years	39	16.53	13.3
30 - 34 years	41	17.37	5.9
35 - 39 years	57	24.15	3.7
40 - years	29	12.29	1.2
Total	236	100.00	100.00
Mean age of nephritic patients			30.14 years
Mean age of total hospital patients			23.86 years

TABLE III. PARITY OF PATIENTS WHEN FIRST SEEN WITH NEPHRITIS

PARA	CASES	PER CENT NEPHRITIC PATIENTS	PER CENT EACH PARA IN
			TOTAL HOSPITAL PATIENTS
0	71	30.08	52.79
1	29	12.29	17.86
2	22	9.32	8.90
3	20	8.47	5.54
4	12	5.08	3.73
5	16	6.78	2.85
6	15	6.36	2.34
7	12	5.08	1.61
8	9	3.81	1.29
9	7	2.97	0.92
10 & over	23	9.75	2.18
Total	236	99.99	100.01

TABLE IV. INCIDENCE OF COMPLICATING DISEASE

Following eclampsia	10	4.24% of patients
Cardiac disease	22	9.32% of patients
Pyelitis	5	2.12% of patients
Syphilis	25	10.59% of patients
Total	62	26.27% of patients

The incidence of pyelitis and of syphilis is not higher than in our nonnephritic clinic patients.

The treatment in the hospital of the 236 nephritic patients is summarized in Table V. This shows that in 96 of them, or 37 per cent, was the pregnancy interrupted, and in 63 per cent of the cases was the patient allowed to proceed to full term. Active interference, either early or late in pregnancy, was therefore practiced in about one-third of the patients. In only 30 cases (12.71 per cent) was future child-bearing rendered impossible by sterilization, either at the time of delivery or during or after the puerperium.

In Table VI, we see the results to the offspring where the mother is suffering from nephritis. In viable babies the mortality is 21.4 per

cent, as compared with 9.5 per cent in the total clinic population. This figure does not include pregnancies terminating in abortions. Furthermore, the table shows that the prognosis for the child becomes proportionately worse with increasing multiparity.

Out of 236 nephritic patients admitted to this service, we were able to trace 135, while no information could be obtained concerning the

TABLE V. PREMATURE TERMINATION OF PREGNANCY

Labor induced near term	43	26.15% 10.77%	Of total nephritic patients delivered
Labor induced premature	25		
Therapeutic abortions	28		

TABLE VI. FETAL MORTALITY ACCORDING TO PARITY OF MOTHER

PER CENT			
Para 0	8 deaths	11.27	
Para 1 and 2	13 deaths	25.49	
Para 3 and 4	10 deaths	31.25	
Para 5, 6 and 7	7 deaths	21.21	
Para 8, 9 and 10	8 deaths	30.77	
FETAL MORTALITY	DEATHS	MORTALITY PER CENT	MORTALITY PER CENT FOR TOTAL HOSPITAL POPULATION
Premature	26	52.00	56.48
Full term	20	12.12	6.33
Total (viable fetus)	46	21.40	9.51

TABLE VII. MATERNAL MORTALITY

Total admissions	297	
Total deliveries	236	
Total traced	135, 57.20% of total patients	
Total dead	46	
Total alive	89	
Total died in hospital	13	
Total died later	33	
Total died, nephritis	37	
Total died, other causes	7	
Total died, cause unknown	2	
Total alive, no nephritis	26	
Total alive, not examined	13	
Total alive, moderate nephritis	20	
Total alive, severe nephritis	30	
Died Nephritis	37, 42.53%	
Alive Nephritis	50	

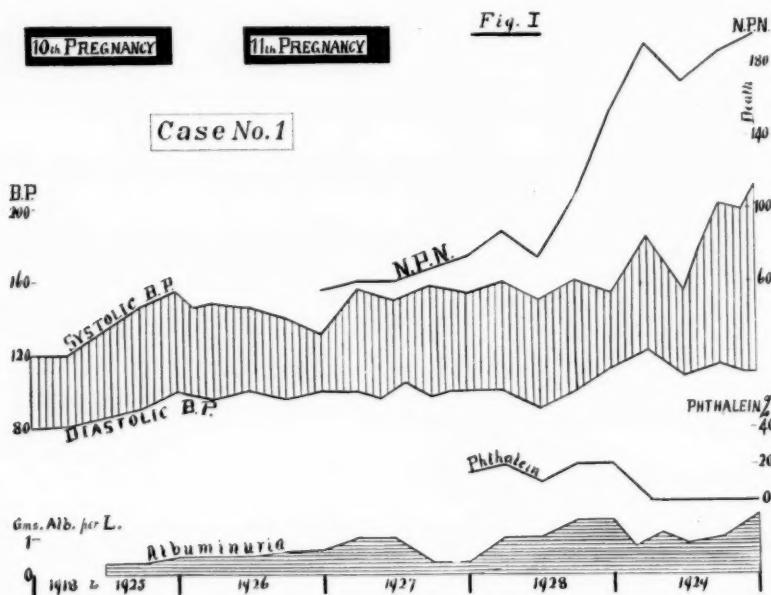
remainder. Of these 135 patients, 46 have died while 89 are still living. Of the 46 deaths, 37 were due to nephritis and 7 to other causes, while in 2 instances the cause of death could not be ascertained, as shown in Table VII. It may be stated here that the cause of death in each case was verified by autopsy or investigation of the death certificate as filed with the local Department of Health.

In Fig. VI, the mortality among the nephritic women is compared with the total death rate in this country for women between the ages of thirty and forty years, as given in the standard statistical life tables.

As most of the patients whom we have been able to trace fall in this age group, we feel that such a comparison is fairly logical.

Our mortality rates for both mother and child in this series are so appallingly high, that we must review the treatment these patients received at our hands. It may be said that we have been far too conservative, and this is amply shown in the charts of the four patients represented in Figs. I, II, III, and IV, all of whom died from nephritis as shown by autopsy.

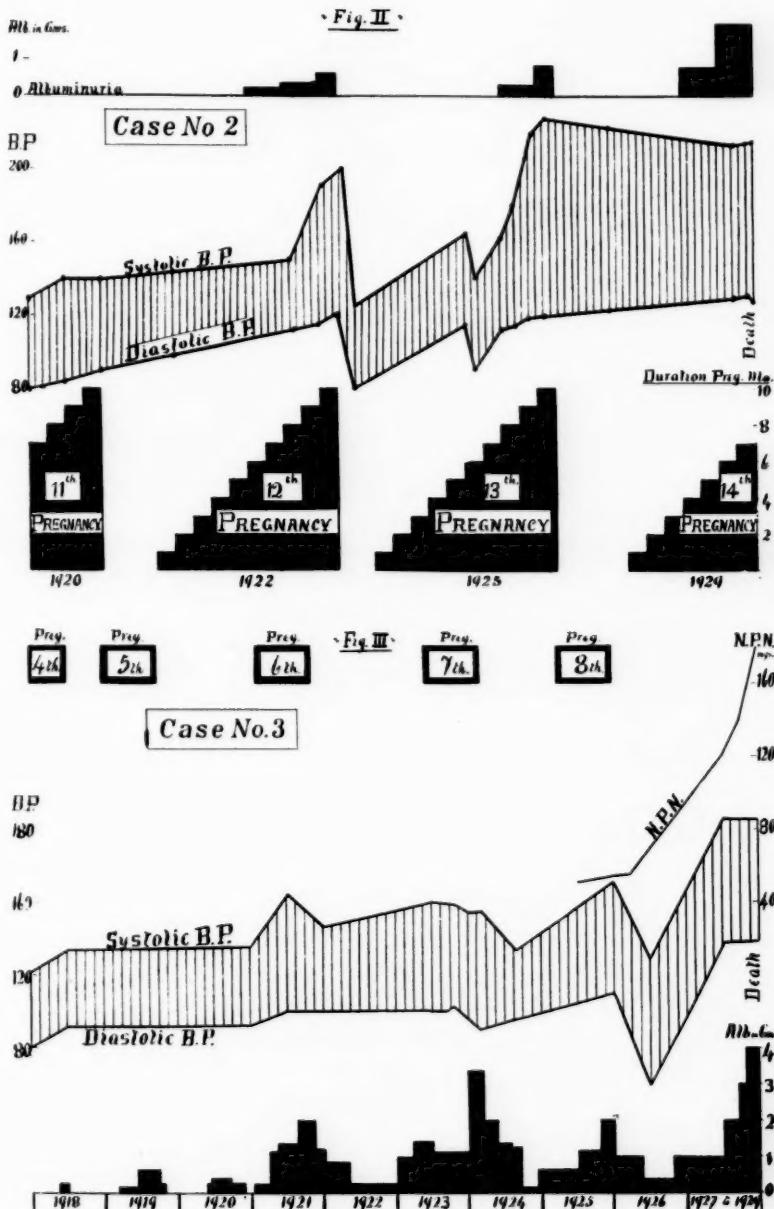
CASE 1.—The first patient, shows a hypertension and albuminuria starting about the middle of her tenth pregnancy. Afterward the blood pressure never returned to normal, nor did the albuminuria disappear. At that time, she presented convincing evidence of kidney damage, yet we allowed her to become pregnant for the



eleventh time, and to proceed to term without interruption. At the middle of the eleventh pregnancy she began to show nitrogenous retention, and from then onward, the downward course was progressive, and death occurred from kidney disease two years later. We feel that this patient should have been sterilized early in her tenth pregnancy.

CASE 2.—Patient (Fig. II), presents an even more incriminating story. In this instance, we had all the necessary evidence of kidney damage in the eleventh pregnancy, yet she was allowed to have three more pregnancies, and died of nephritis during the latter half of her fourteenth pregnancy. It is interesting to note that in this case after the twelfth pregnancy the blood pressure dropped to a normal systolic and an only slightly elevated diastolic, while the albuminuria disappeared. There is, perhaps, some excuse for not having sterilized her after this delivery, although the behavior of the blood pressure during and after the eleventh pregnancy would indicate the existence of a nephritis rather than preeclampsia. There is, however, no justification for allowing this patient to proceed from a thirteenth to a fourteenth pregnancy.

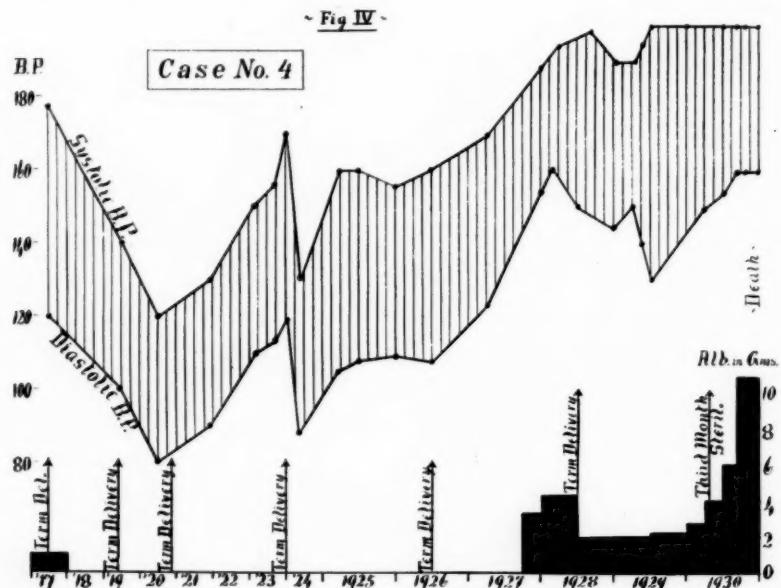
CASE 3.—Patient (Fig. III) had a diastolic blood pressure of 90 or above from the end of her fourth pregnancy, and a permanent albuminuria from her sixth pregnancy on; yet she went through two additional pregnancies, dying three years after her last confinement.



CASE 4.—(Fig. IV.) We saw a blood pressure of 180/120 at the end of the first pregnancy in this patient. From the behavior of the blood pressure and albuminuria following this pregnancy, it is probable that she suffered from preeclampsia at that time; but there was certainly no reason to doubt the existence

of a chronic nephritis following the fourth pregnancy; yet she was allowed to become pregnant three more times, with a blood pressure ranging around 160/110 and 200/140 following the fifth and sixth pregnancy, reaching 200/150 at the third month of her seventh and last pregnancy.

These four patients were selected at random from the women who have died on our service from chronic nephritis. We feel from the evidence presented in the charts that our treatment in these cases, as well as in many other nephritic patients, has been too conservative. It furthermore seems to us that the added strain of repeated pregnancy in women who present signs of kidney damage, must inevitably aggravate the disease and shorten the life of the patient. This is further evidenced by the increasing incidence of nephritis as multiparity proceeds, as shown in Fig. V.

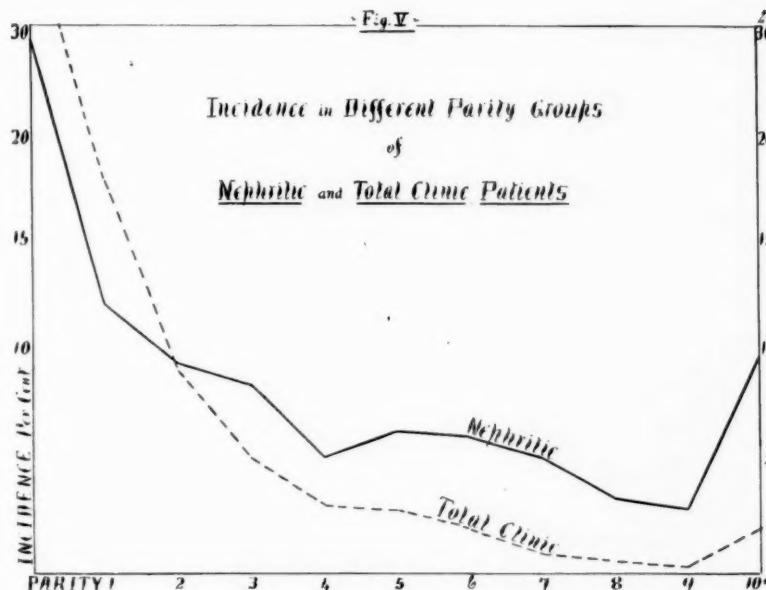


In the 135 women traced, we found that 26 or 19.27 per cent have no demonstrable sign or symptom suggesting the existence of chronic nephritis at present, thus indicating that the original diagnosis was incorrect. Of the remaining 109 patients, 46 are dead, 30 have severe nephritis, 20 are suffering from moderate but definite kidney damage, while in 13 cases we have been unable to obtain information beyond the fact that they are alive.

It seems, therefore, that over 80 per cent of our diagnoses of chronic nephritis were correct, whereas in one case out of five, we have diagnosed a chronic nephritis when we were dealing actually with a low reserve kidney or in rare instances with preeclampsia. We are of the opinion that with closer study this percentage of mistaken diagnosis may be decreased, but on the other hand we feel that this type of error

in diagnosis is not as grave as failure to recognize the existence of a chronic nephritis. If we must err in diagnosis in a small fraction of our patients, it would seem preferable to designate an occasional case of low reserve kidney as nephritis, rather than the reverse.

We do not wish to discuss the many factors that may be of help in the diagnosis of chronic nephritis, which will be considered in a later paper, but we cannot refrain from commenting upon a few points. The presence of albuminuria is not essential to the diagnosis, nor is it necessary that the patient have such symptoms as headache, visual disturbances, or malaise. In most of the fatal cases of nephritis in this series the patients had no, or very slight, symptoms or complaints



until shortly before the nitrogenous retention became marked and the terminal stage was reached. Too much emphasis should not be placed on symptoms, or rather, the absence of symptoms.

Persistent hypertension without albuminuria and symptoms is sometimes misleading, and the so-called "essential hypertension" has often lured the physician into a false sense of security. We view with great concern any patient showing hypertension persisting for several months following pregnancy provided other causative factors are eliminated, even though albuminuria, edema and symptoms are absent. We feel that signs of serious renal involvement will ultimately appear in such cases, although for some time these patients may reveal no sign or symptom beyond the hypertension.

Pregnancy is undoubtedly one of the best kidney function tests, as it exerts a slowly but steadily increasing strain on these organs. At

present, we possess no adequate method of measuring this added work, but it must be of considerable magnitude as is evidenced by the large percentage of women who have apparently normal kidneys while not pregnant but show signs of decreased kidney function as a pregnancy appears and proceeds to term.

We are not able to state that our patients with chronic nephritis would not die from the disease were they not allowed to become pregnant, but we are strongly of the opinion that the added strain of pregnancy, and especially of repeated pregnancies, must inevitably hasten the end.

In view of the large maternal mortality and the very poor prognosis for the offspring in the series of patients studied, we advocate interference with birth control or actual sterilization rather than conservative and expectant treatment in a large percentage of pregnant women with definite chronic nephritis. No universal rule can be laid down, but we feel that where there is no doubt that a chronic nephritis exists, it is our duty to prevent the strain of pregnancy and we are justified in following conservative treatment only when the patient is anxious to assume the responsibility on personal or other grounds.

We have been very strongly impressed and surprised with the outstanding finding of this study of the end-results in chronic nephritis initiated or aggravated by pregnancy; and that is, a death rate, immediate and within a relatively short period of time, of 42.5 per cent among the mothers. A study of the 37 deaths from chronic nephritis showed the following results:

TABLE VIII

YEAR SEEN WITH NEPHRITIS	DIED IN CLINIC	DIED OUTSIDE	
		NUMBER	YEARS LATER
1919	0	1	5
1920	0	2	2, 4
1921	1	3	4, 5, 6
1922	2	3	3, 4, 5
1923	0	3	2, 6, 6
1924	1	2	4, 6
1925	3	4	1, 3, 3, 4
1926	0	1	4
1927	0	3	2, 2, 2
1928	3	5	1, 1, 2, 2, 2
Total	10	27	3.37 average years

We have not attempted to study the actual duration of chronic nephritis in each fatal case, as such an undertaking is an almost impossible task due to the difficulty of establishing the date of the first appearance of the disease. However, as the duration of life in the patients dying outside the hospital, after a diagnosis of nephritis had been made in the hospital, averaged only 3.37 years, and in addition 27 per cent of the patients who died had died while in this hospital,

the prognosis in patients showing signs of kidney damage during a pregnancy is indeed very grave and far more so than we had formerly believed. The effect of pregnancy on chronic nephritis is further illustrated by the fact that further pregnancies were allowed in many of the cases which later terminated fatally, whereas in only 4 of the 50 nephritic women now alive had a pregnancy subsequent to the one in which the diagnosis of nephritis was made. It seems significant that the duration of life to date in the living women is now 6.12 years, a figure almost twice that of the duration of life in the fatal cases, so many of whom had become pregnant after chronic nephritis had been diagnosed by us.

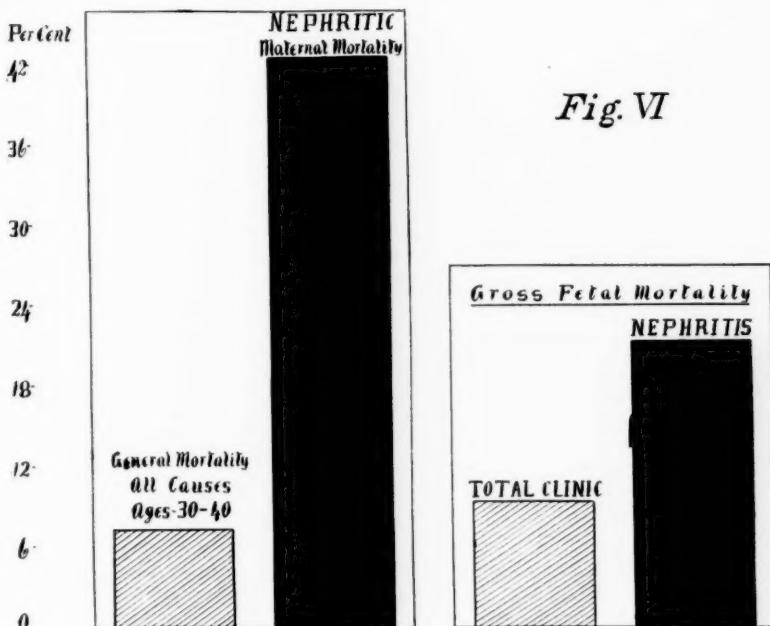


Fig. VI

## CONCLUSIONS

1. Chronic nephritis usually manifests itself during the later years of the child-bearing period, as is evidenced by the fact that over half of the patients in our series are over thirty years of age, while only one-tenth of the total clinic patients are in this age group.
2. There appears to be a definite correlation between the incidence of nephritis and increasing parity. Although 80 per cent of the total clinic patients are either primiparae or have had one previous pregnancy, only 42 per cent of the nephritic women fall into this category.
3. We have observed a surprisingly small incidence of concomitant cardiac disease (9.3 per cent) and pyelitis (2.1 per cent) in our series of nephritic women.

4. The absence of albuminuria, edema, symptoms, and signs of decreased kidney function in the presence of a hypertension, does not speak against the existence of an underlying or developing chronic nephritis. The term "essential hypertension" as denoting no kidney damage is a dangerous one to employ as the hypertension may be the first sign to precede the development of serious renal impairment dependent upon arteriosclerotic changes in the kidneys.

5. The fetal mortality in our series of nephritic women is over 21 per cent in viable babies, as compared with 9.5 per cent for all patients in our clinic.

6. The maternal mortality occurring within ten years in our series is appallingly high, being 42.53 per cent. The average mortality for women between the ages of thirty and forty years in this country is 7.5 per cent.

7. The added strain of pregnancy on renal function undoubtedly aggravates an underlying or existing chronic kidney disease, and must often materially shorten the patient's life.

8. The prognosis in chronic nephritis complicating pregnancy is very grave, the average duration of life after definite diagnosis had been made, being only three and thirty-seven hundredths years in the fatal cases. On the other hand, only 4 of the 50 nephritic women now alive have had subsequent pregnancies and to date their average duration of life is six and twelve hundredths years, following the diagnosis of chronic nephritis.

9. We advocate more radical treatment than has been exercised in the care of the patients in our series. In the presence of a definite chronic nephritis it is usually advisable to terminate pregnancy and prevent further pregnancies by either birth control or sterilization, depending upon the individual case.

10. The time to prevent kidney strain from pregnancy is not after a chronic nephritis has become severe, but while it is still mild in character, or in its incipiency, for then only can we hope to be of assistance to our nephritic patients.

## THE BLOOD SUGAR IN ECLAMPSIA

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(From the Dept. of Obstetrics, St. Mary's Hospital)

THE exact etiology of the symptom complex called eclampsia is still unsolved. The work of many earnest investigators of this problem would indicate that it is a disease due to a disorganization of the maternal metabolism which is instigated by pregnancy.

Titus<sup>1</sup> and his coworkers have advanced the theory that a glucose deficiency of the body is the causative factor, and in favor of this viewpoint we have the following facts additional to or amplifying those he has presented: (1) a depletion of the reserve carbohydrate, glycogen, is found postmortem in all cases of eclampsia; (2) the fetus is known to derive its nourishment largely from the carbohydrate in the mother's blood; (3) the pituitary, adrenals, thyroid, and pancreas, all of which have a proved influence on the carbohydrate metabolism, are characteristically altered during pregnancy; (4) the intravenous administration of glucose is of great value in the treatment of various toxemias including eclampsia, a fact first noted by Titus<sup>1</sup> and later confirmed by many clinics.

If the carbohydrate metabolism is profoundly disturbed it is reasonable to assume that the blood sugar should reflect this disturbance in some manner and Titus<sup>2</sup> has shown that if the blood is examined at five-minute intervals there is, (1) a marked and significant fluctuation in the blood-sugar level; (2) a drop in the blood sugar from a higher to a lower level preceding a convulsion; (3) a rise in the blood-sugar level is noted following a convulsion; (4) subnormal blood-sugar levels are frequently noted.

A few investigators, notably Stander and Harrison<sup>3</sup> of the Johns Hopkins Hospital have attempted to discredit the work of Titus without making an effort to repeat it. They contend that because a high blood sugar is not infrequently found during the course of an eclamptic attack that a hyperglycemia is characteristic of this disease, without regard to the well-known fact that any muscular exertion even less severe than an eclamptic convulsion is followed physiologically by hyperglycemia. They have recommended the use of insulin because of this hyperglycemia which is obviously physiologic and temporary, a therapy which is certainly questionable if a glucose deficiency of the body exists.

Titus claims that a glucose deficiency of the body is the cause of eclampsia and the blood-sugar findings in this disease show a profound disturbance of the carbohydrate metabolism. The blood-sugar

level normally ranges between 80 and 120 mg. per 100 c.c. and some mechanism operates to maintain this level probably by increasing the production of insulin if it goes too high and by releasing glucose into the blood from the reserve stored in the liver if it drops too low; in starvation the blood-sugar level is lower but this lower level is maintained by the body converting some of its proteid into glucose; if the blood sugar falls below a certain point convulsions and death ensue.

Cori and Cori<sup>4</sup> have recently shown that during severe muscular exertion and in a deficiency of oxygen, adrenalin causes the glycogen stored in the muscles to be incompletely oxidized into lactic acid and that this lactic acid was reconverted into glucose by the liver. In pregnancy any of the following conditions or their combinations may operate to produce a disturbance of the carbohydrate balance: (1) a continuous and increasingly heavy withdrawal of glucose from the maternal blood to nourish the products of conception; (2) an excessive consumption of glucose by the maternal organism; (3) excessive withdrawal of glucose from the maternal blood due to overproduction of insulin; (4) an inadequate supply of glucose due to faulty alimentation.

With these facts relative to the carbohydrate metabolism in mind, we can now picture theoretically the sequence of events in minor toxemias and eclampsia: we have a disturbance of the carbohydrate balance due to one or more of the conditions mentioned, the excess of glucose withdrawn being replenished from the reserve stored in the liver until that is exhausted, then an attempt is made to supply the increasing deficiency by manufacturing glucose from the body protein; this supply proving inadequate and the deficiency becoming acute, as a last effort, we have the eclamptic fit which by releasing, as lactic acid, the glycogen stored in the muscles, supplies material which the liver can quickly convert into glucose.

The blood-sugar level at any one reading merely shows the status at the time the blood was withdrawn and to obtain a true picture of the process it is necessary that frequent examinations be made. The changes occur rapidly and hence the specimens should be withdrawn at short intervals of time. Until the process is stabilized or until the available glucose reserve is depleted there should be more normal and above normal readings than subnormal. Subnormal values will be obtained in all cases at some time if a sufficient number of examinations are made.

The following study of the blood sugar in eclampsia repeats the work of Titus and corroborates his findings regarding the fluctuation in blood sugar during eclampsia with relative hypoglycemic levels before the convulsions. The cases, 10 in number, are from the serv-

ices of Drs. J. Stuart Lawrence at St. Mary's Hospital, and George Hanna at Frankford Hospital. All data have been depleted from the case histories except that relevant to the present study, for the sake of brevity. The blood-sugar examinations were made in the laboratory of St. Mary's Hospital, in charge of Dr. William Reese, and were made by the method of Folin and Wu, which gives a normal range between 80 and 120 mg. per 100 c.c. The examinations were usually made immediately after the blood was taken and in no instance later than four hours after the blood was withdrawn, calcium oxalate being used as an anticoagulant.

In 6 of the 10 cases the examinations were made at five-minute intervals, in one case at ten-minute intervals, in one case at half-hour intervals and in two cases at irregular intervals.

CASE 1.—St. Mary's Hospital, 1930. Antepartum Eclampsia. Recovered.

8:30 A.M. First convulsion.  
9:00 A.M. Second convulsion.  
9:40 A.M. Third convulsion.  
9:55 A.M. Fourth convulsion.  
10:55 A.M. Fifth convulsion.  
11:40 A.M. Sixth convulsion.  
11:41 A.M. First blood sugar 160 mg. per 100 c.c.  
11:45 A.M. Second blood sugar 145 mg. per 100 c.c.  
11:50 A.M. Third blood sugar 130 mg. per 100 c.c.  
11:55 A.M. Fourth blood sugar 100 mg. per 100 c.c.

Patient had a total of 13 convulsions.

COMMENT

1. Blood examined one minute after sixth convulsion and three hours and eleven minutes after onset.
2. Fluctuations 15 to 30 mg.
3. Note high blood sugar one minute after convulsion, also drop of 60 mg. in fifteen minutes.
4. Few examinations and no readings below normal.

CASE 2.—St. Mary's Hospital 1930. Antepartum Eclampsia. Died.

1:30 A.M. First convulsion.  
3:40 P.M. Second convulsion.  
4:10 P.M. Third convulsion.  
4:30 P.M. First blood sugar 73 mg. per 100 c.c.  
4:50 P.M. Second blood sugar 93 mg. per 100 c.c.  
4:55 P.M. Third blood sugar 80 mg. per 100 c.c.  
5:00 P.M. Fourth blood sugar 88 mg. per 100 c.c.  
5:05 P.M. Fifth blood sugar 90 mg. per 100 c.c.  
5:07 P.M. Fourth convulsion.  
5:10 P.M. Sixth blood sugar 81 mg. per 100 c.c.  
5:15 P.M. Seventh blood sugar 87 mg. per 100 c.c.  
5:17 P.M. Fifth convulsion.

Patient had a total of 19 convulsions before death thirty hours later.

## COMMENT

1. Blood was examined twenty minutes after third convulsion and fifteen hours after onset examinations were made at five-minute intervals.
2. Note low normal and one subnormal reading during period of active convulsions.
3. The convulsion at 5:07 P.M. did not show any drop two minutes before, but the values being low a significant drop may have occurred in these two minutes. That such a drop did occur is suggested by the low reading three minutes later. This low blood sugar so soon after a convulsion shows either a badly damaged liver or a very low reserve.

CASE 3.—St. Mary's Hospital 1930. Antepartum Eclampsia. Recovered.

8:45 A.M. First convulsion.  
11:45 A.M. Second convulsion.  
11:55 A.M. First blood sugar 73 mg. per 100 c.c.  
12:00 P.M. Second blood sugar 104 mg. per 100 c.c.  
12:05 P.M. Third blood sugar 91 mg. per 100 c.c.  
12:15 P.M. Fourth blood sugar 98 mg. per 100 c.c.  
12:20 P.M. Fifth blood sugar 93 mg. per 100 c.c.

Patient had a total of 4 convulsions.

## COMMENT

1. Blood examinations were made after second convulsion and three hours and ten minutes after onset of disease, examinations were made at five-minute intervals.
2. Fluctuations 5 to 31 mg.
3. One subnormal reading, the others within normal range.

CASE 4.—Frankford Hospital 1928. Antepartum Eclampsia. Died.

6:30 A.M. Admitted to hospital in coma with history of having 7 convulsions since 1:30 A.M.  
8:30 A.M. First blood sugar 125 mg. per 100 c.c.  
8:31 A.M. 25 gm. glucose given intravenously.  
9:45 A.M. 50 gm. glucose given intravenously.  
9:50 A.M. Eighth convulsion.  
10:20 A.M. Second blood sugar 74 mg. per 100 c.c.  
10:25 A.M. Third blood sugar 92 mg. per 100 c.c.  
10:30 A.M. Fourth blood sugar 89 mg. per 100 c.c.  
10:33 A.M. Ninth convulsion.  
10:35 A.M. Fifth blood sugar 145 mg. per 100 c.c.  
10:40 A.M. Sixth blood sugar 129 mg. per 100 c.c.  
10:50 A.M. Seventh blood sugar 128 mg. per 100 c.c.  
10:55 A.M. Eighth blood sugar 122 mg. per 100 c.c.  
11:00 A.M. Ninth blood sugar 93 mg. per 100 c.c.  
11:05 A.M. Tenth blood sugar 70 mg. per 100 c.c.  
11:30 A.M. Tenth convulsion.

Patient had a total of 18 convulsions before death.

## COMMENT

1. Blood was examined after eighth convulsion and after 75 gm. of glucose had been given intravenously. Eight hours and fifty minutes after onset.
2. The sugar was apparently being withdrawn from the blood very rapidly because although patient was given 75 gm. glucose intravenously and had one convulsion within less than two hours the blood sugar was only 74 mg.

3. The blood sugar showed a slight drop at 10:30 which probably became great enough to precipitate the convulsion three minutes later. Note the rise in blood sugar two minutes after the convulsion.

4. The steady dropping of the blood sugar is clearly shown between 10:35 and 11:05, 75 mg. in a half hour and culminating in the convulsion at 11:10.

CASE 5.—Frankford Hospital 1929. Postpartum Eclampsia. Recovered.

6:30 A.M. Admitted to hospital with history of having two convulsions at home.

10:05 A.M. First blood sugar 51 mg. per 100 e.e.

10:10 A.M. Second blood sugar 41 mg. per 100 e.e. (Patient observed to twitch.)

10:15 A.M. Third blood sugar 73 mg. per 100 e.e.

10:20 A.M. Fourth blood sugar 46 mg. per 100 e.e.

10:25 A.M. Fifth blood sugar 49 mg. per 100 e.e.

10:30 A.M. Sixth blood sugar 75 mg. per 100 e.e.

Patient had only two convulsions, both before admission to hospital.

#### COMMENT

1. Blood examined at five-minute intervals. Fluctuations 2 to 32 mg.

2. Note extremely low values.

CASE 6.—Frankford Hospital 1930. Postpartum Eclampsia. Recovered.

7:05 A.M. First convulsion (8 hr. postpartum).

8:30 A.M. Second convulsion.

9:20 A.M. Third convulsion.

9:55 A.M. First blood sugar 71 mg. per 100 e.e.

10:00 A.M. Second blood sugar 72 mg. per 100 e.e.

10:05 A.M. Third blood sugar 67 mg. per 100 e.e.

10:10 A.M. Fourth blood sugar 73 mg. per 100 e.e.

10:15 A.M. Fifth blood sugar 67 mg. per 100 e.e.

10:22 A.M. Sixth blood sugar 55 mg. per 100 e.e. (Patient observed to twitch.)

10:29 A.M. Seventh blood sugar 69 mg. per 100 e.e.

10:45 A.M. Fourth convulsion.

Patient had six convulsions on first day, four days later she had 2 convulsions, the following day she had 5 convulsions, and two days later she had 3 convulsions, a total of 16 convulsions over a period of seven days. Patient was a deaf mute.

#### COMMENT

1. Blood was examined two hours and fifty minutes after onset and after third convulsion and at five- to seven-minute intervals.

2. Fluctuations 1 to 14 mg.

3. All readings below normal.

CASE 7.—St. Mary's Hospital 1928. Postpartum Eelampsia. Recovered.

June 17, 11:00 P.M. Patient admitted to hospital with a history of having five convulsions at home, the first at 5:00 A.M., eight hours postpartum and the others at 5:10 and 9:00 A.M., and at 1:30 and 9:00 P.M.

11:15 P.M. First blood sugar 70 mg. per 100 e.e.

June 18, 12:24 A.M. Seeond blood sugar 135 mg. per 100 e.e.

12:34 A.M. Third blood sugar 130 mg. per 100 e.e.

12:44 A.M. Fourth blood sugar 125 mg. per 100 e.e.

12:54 A.M. Fifth blood sugar 120 mg. per 100 e.e.

1:09 A.M. Sixth blood sugar 118 mg. per 100 e.e.

1:19 A.M. Seventh blood sugar 110 mg. per 100 e.e.  
1:24 A.M. Eighth blood sugar 97 mg. per 100 e.e.  
2:00 A.M. Ninth blood sugar 138 mg. per 100 e.e.  
2:08 A.M. Tenth blood sugar 142 mg. per 100 e.e.  
2:15 A.M. 100 gm. glucose given intravenously.  
2:25 A.M. Eleventh blood sugar 150 mg. per 100 e.e.

Patient had a total of five convulsions before admission, none after.

#### COMMENT

1. Blood-sugar estimations made mostly at ten-minute intervals. The first was made eighteen and one-quarter hours after onset and after fifth convulsion.
2. Fluctuations in blood sugar values 5 to 65 mg.
3. One reading below normal.
4. Note steady drop from 12:24 to 1:24, then raise in next thirty-six minutes.
5. Note how quickly the glucose is withdrawn from the blood, the blood sugar at 2:25 was only 150 mg., ten minutes after 100 gm. glucose had been given intravenously, seven minutes before giving glucose it was 142 mg.

CASE 8.—St. Mary's Hospital 1930. Postpartum Eclampsia. Recovered.

April 15, 11:00 A.M. Admitted to hospital, had fourth convulsion just after admission and with a history of having 3 convulsions at home  
The first at 1:30 P.M. and the second at midnight April 14  
The third convulsion occurred at 8:00 A.M. April 15.  
3:00 P.M. Fifth convulsion.  
3:30 P.M. 25 gm. glucose given intravenously.  
3:45 P.M. 25 gm. glucose given intravenously.  
4:15 P.M. First blood sugar 42 mg. per 100 e.e.  
4:15 P.M. Sixth convulsion (just as blood was being taken).  
4:45 P.M. Second blood sugar 38 mg. per 100 e.e.  
4:57 P.M. Third blood sugar 42 mg. per 100 e.e.  
5:14 P.M. Fourth blood sugar 36 mg. per 100 e.e.  
5:15 P.M. Seventh convulsion.  
5:16 P.M. Fifth blood sugar 42 mg. per 100 e.e.  
5:22 P.M. Sixth blood sugar 39 mg. per 100 e.e.

#### COMMENT

1. Blood examined at irregular intervals and fluctuation was slight 4 to 7 mg.
2. All examinations showed extremely low blood-sugar values.
3. Very little rise after the convulsion was noted, also very little drop before.
4. Patient was given glucose before examinations were made.

CASE 9.—Frankford Hospital 1929. Antepartum Eclampsia. Died.

1:30 A.M. Admitted to hospital in coma. Had convulsion just after admission.  
1:35 A.M. 25 gm. glucose given intravenously.  
2:10 A.M. Convulsion.  
2:20 A.M. Blood sugar 180 mg. per 100 e.e.  
2:35 A.M. Convulsion.  
3:00 A.M. Convulsion.  
3:40 A.M. Blood sugar 285 mg. per 100 e.e.  
3:50 A.M. Convulsion.  
4:00 A.M. Convulsion.

4:10 A.M. Blood sugar 110 mg. per 100 e.e.  
4:20 A.M. Convulsion.  
4:40 A.M. Blood sugar 100 mg. per 100 e.e.  
4:45 A.M. Convulsion, 5:25 A.M. convulsion, and 5:45 A.M. convulsion.  
7:00 A.M. 25 gm. glucose given.  
7:30 A.M. Convulsion, 8:00 A.M. convulsion, and 11:00 A.M. convulsion.  
12:15 P.M. Blood sugar 77 mg. per 100 e.e.  
12:30 P.M. Convulsion, 1:00, 2:00, and 3:15 P.M. convulsion.  
4:00 P.M. 25 gm. glucose given intravenously.  
4:15 P.M. Convulsion.  
5:25 P.M. Blood sugar 107 mg. per 100 e.e.  
5:30 P.M. Convulsion.  
5:31 P.M. Blood sugar 115 mg. per 100 e.e.  
5:45 P.M. Blood sugar 97 mg. per 100 e.e.  
5:46 P.M. Convulsion.  
6:40 P.M. Blood sugar 97 mg. per 100 e.e.  
7:00 P.M. Convulsion.

Patient had a total of 27 convulsions before death.

#### COMMENT

1. Blood examined at irregular intervals.
2. One reading slightly below normal 77 mg. at 12:15 P.M.
3. Note the gradual dropping in level from 180 and 285 mg. to 97 mg. as the disease progressed.

#### CASE 10.—Frankford Hospital. Postpartum Eclampsia. Recovered.

March 10, 1930, 10:30 P.M. Admitted to hospital with history of having 4 convulsions since noon.

11:00 P.M. Blood sugar 220 mg. per 100 e.e.  
12:00 P.M. Fifth convolution.

March 11, 1930, 12:30 P.M. Sixth convolution.

1:00 P.M. Seventh convolution.  
3:00 P.M. Eighth convolution.  
4:00 P.M. Ninth convolution.  
6:00 P.M. Tenth convolution.  
7:20 P.M. Eleventh convolution.  
8:40 P.M. Twelfth convolution.  
10:00 P.M. Thirteenth convolution.  
11:15 P.M. Blood sugar 140 mg. per 100 e.e.  
11:45 P.M. Blood sugar 140 mg. per 100 e.e.  
12:15 P.M. Blood sugar 90 mg. per 100 e.e.  
12:45 P.M. Blood sugar 110 mg. per 100 e.e.  
1:15 P.M. Blood sugar 160 mg. per 100 e.e.  
1:45 P.M. Blood sugar 162 mg. per 100 e.e.

Patient had a total of 13 convulsions.

#### COMMENT

1. Blood was examined at thirty-minute intervals and showed fluctuations of from 0 to 50 mg.
2. All examinations showed normal or above normal values.
3. Patient was recovering when examinations were made.

## SUMMARY OF CASE REPORTS

1. All cases showed significant fluctuations in blood-sugar levels except Case 8; in this case the blood was examined at irregular intervals and all values were very low.
2. Eight of the ten cases showed one or more readings below normal. In the two cases where no subnormal readings were noted one had only four examinations and the other was recovering from the disease.
3. A definite tendency for the blood-sugar level to drop before a convulsion was noted in all cases when the examinations were made while the convulsions were occurring.
4. A rise in blood sugar was noted to follow the convulsion in Cases 1, 4, and 9.
5. That the blood sugar is removed from the circulation very rapidly is shown in Cases 1, 4, 7, 9.
6. A failure of the blood-sugar level to rise after a convulsion, and also a definite tendency to a lower blood-sugar level was noted in those cases where the process had lasted some time.

## CONCLUSIONS

1. The glucose deficiency theory of Titus' offers a rational explanation for most of the phenomena observed in eclampsia, and it will probably prove to be, when more data in reference to the biochemistry of the body are available, at least in part the explanation of this perplexing disease.
2. The convulsion in eclampsia is part of the body mechanism for combating a glucose deficiency and hence should be considered a protective reaction just as fever, vomiting and dyspnea are protective reactions.
3. The present study corroborates the work of Titus on the blood-sugar findings in eclampsia.
4. Stander's<sup>3</sup> article in disagreement with this does not constitute a valid criticism of the work done by Titus as no attempt was made to duplicate his researches.

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## IS SALPINGITIS A FACTOR IN THE INCIDENCE OF TUBAL PREGNANCY?\*

BY ROYAL C. VAN ETEN, M.D., F.A.C.S., NEW YORK, N. Y.

MANY theories have been advanced to explain ectopic formation, including salpingitis, retroversion, fibroids, kinking of the tubes by bands, the presence of accessory tubes or diverticula.

"It is generally believed that inflammation of the fallopian tubes by narrowing the lumen and in this way preventing the passage of the impregnated ovum to the uterus, is an important etiologic factor in ectopic gestation." Thus wrote H. C. Taylor, in a review of cases at the Roosevelt Hospital, New York, from 1909 to 1914. Of the 44 cases so reported, 76 per cent gave a history of inflammation of the appendages, or it was discovered at operation. Other writers give the following figures: Franz, 80 per cent; Prochonsk, 50 per cent; Schurman, 50 per cent; Falk, 33 per cent (50 cases).

These figures may seem to us very high and yet they can be still further raised if the cases are considered in which peritoneal adhesions were found. In almost every case, some bands and adhesions can be found. Tubes diseased by neisserian infection head the list, but tuberculous tubes are not infrequent.

With these figures in mind, I looked up the cases of tubal pregnancy occurring at the Sloane Hospital for Women for the last five years. This list includes all patients with ectopic pregnancies admitted to the hospital. A full pathologic report accompanied each one, so it was comparatively easy to get our conclusions from the charts themselves, and by personal talks with the members of the Staff.

Since 1926 and including 1930 to date, we have had 77 cases of tubal pregnancy in the hospital. Our findings differ from most of those above, in that only 8 cases, or 10.4 per cent showed signs of previous or concurrent tubal inflammation. When peritoneal adhesions were considered, a total of 20, or 27.7 per cent, was found. If both are taken together, a total of 28, or 36.3 per cent, was found. We had one case of tuberculous tubes and one remarkable case where a firm band of adhesions from the uterus itself to the peritoneum had caused a kinking of the tubes and probably an ectopic pregnancy.

Ahlfeld gives an interesting side light on this situation by stating that in an experience of many years at the University of Marburg, he saw so few cases of tubal gestation that he considers the relative freedom of his patients from gonorrhea, as compared with those in the large cities, to be the only explanation.

\*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, December 23, 1930.

We have tabulated all the details of our 77 cases. The pathologist states that a section through the affected tube near the site of an ectopic gestation, and especially where one has ruptured, gives a picture very similar to inflammation, with outpouring of round cells and leucocytes from the mother's blood. Recent adhesions and inflammatory reaction in addition to the hemorrhage are also seen. These pictures have doubtless deceived many in their reports as to the presence of inflammation in the tubes. Moreover, we all know how clear the other tube and its fimbriated extremity appears in a majority of instances at the time of operation, after we have cleared the clots away from it. Fourteen of our cases were unruptured at the time of operation, 63 ruptured.

It is of interest to note here that 2 of our 77 patients had repeated ectopic pregnancies, although none had concurrent ectopic and intrauterine gestation, as reported by Stein.—One case: Vineberg, Brooks Wells, Keyes, Frankenthal, Young, Zinke, Haret; in instances, from 2 to 5, and Rongy, 12 in 100 cases.

It is also of interest to note that 16 of our patients received one transfusion and 3 two transfusions. Naturally, 10 of these were done in the last two years, as transfusions became more usual.

#### SUMMARY

1. The evidence in favor of previously existing inflammation was rather limited in our series of 77 cases, covering five years at the Sloane Hospital. Eight cases, or 10.4 per cent of 77, showed such evidence.
2. The pathologic picture is often misleading. Sections of the tubes remote from the lesions should always be taken.
3. The majority of our ectopic cases had had no previous inflammation or coexisting inflammation in the tubes.
4. This is contrary to the usually accepted beliefs.

## A CASE OF RUDIMENTARY CONGENITAL HEART IN NEWBORN\*

BY J. IRVING KUSHNER, M.D., NEW YORK, N. Y.

(From the Obstetric Service and the Pathological Laboratory of the Bronx Hospital)

THE mother of this child was twenty-nine years of age. She was one of a family of seven, all of whom were living except one who died at two weeks of age of smallpox and one who died during the influenza epidemic of 1918. The patient weighed 132 pounds, and was strong, healthy, and well nourished. Her past history was entirely negative. Her previous pregnancy had resulted in a normal living male child, three years of age.

The father was thirty years of age and belonged to a family of four boys. He weighed 156 pounds and had always been well and strong. The Wassermann reaction was negative in both parents.

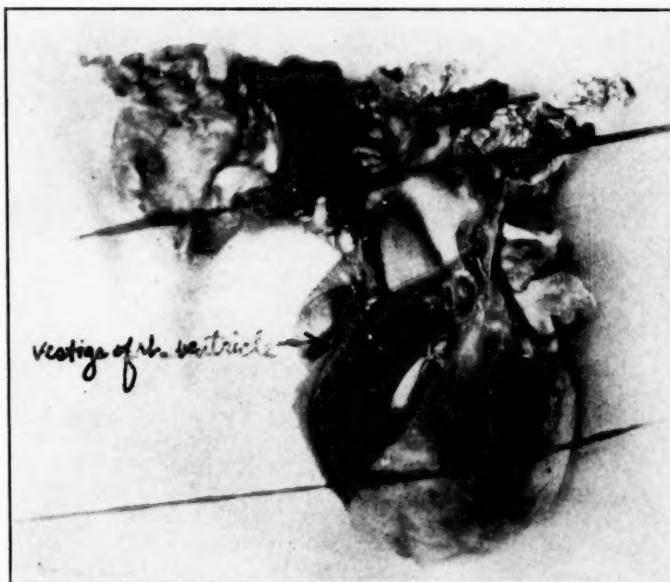


Fig. 1.

The pregnancy was normal in every way. The mother went into labor about 4 A.M., with pains every thirty minutes. These pains continued irregularly until 8 or 9 A.M. when they began to grow stronger and more frequent until she delivered herself at 2 P.M. of a female child, weighing 7 3/4 pounds. There was a little difficulty in the resuscitation of the baby because of three coils of cord around its neck; but the infant was put to bed breathing normally and crying lustily.

It was early noticed that the baby's face was slightly cyanotic but no attention was paid to that because it was attributed to the coils of cord that had been around the infant's neck at birth. The next morning, however, the cyanosis had spread

\*Presented at a meeting of the Bronx Gynecological and Obstetrical Society, November 24, 1930.

all over its body and that on the face had become deeper in color. Examination showed a to and fro sawing murmur at the tricuspid area. The heart was not enlarged to percussion. There were no thrills palpable. The lungs, abdomen and head were all negative. A diagnosis of patent foramen ovale "blue baby" was made.

The baby did well for three days; then it began to have periods of increasing apnea. At the end of the third day it died in one of these attacks despite all efforts at stimulation. The diagnosis at death was asphyxia due to a patent foramen ovale.

The autopsy was done by Dr. S. A. Goldberg.

There were a few macular spots over the body, more on the abdomen, and the infant was slightly bluish. The ears, nose, and mouth appeared normal. The cord had dried and the umbilicus was negative.

In the abdominal cavity the position of the organs was normal and the viscera showed nothing pathologic. There were two bodies probably hemolymph nodes in the splenic omentum.

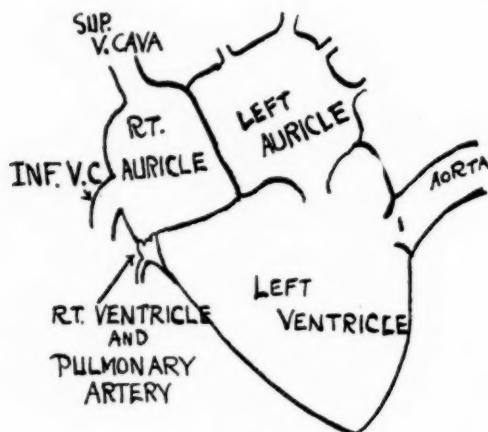


Fig. 2.

There was a moderate amount of pericardial fluid; clear and yellowish. The heart was markedly enlarged and there were subepicardial hemorrhages in the coronary sulci. The heart itself showed left ventricular concentric hypertrophy; the foramen ovale was not patent; the tricuspid valve was completely stenotic measuring 2 mm.; the mitral valve had a hematoma about 3 mm. in diameter near its edge. There was only a vestige of the right ventricle which showed the *corda tendinae* massed together in a lumen about 3 mm. in diameter. The pulmonary artery was extremely small, about 2 mm. in cross-section.

The lungs were normal and floated in water. The thymus was not enlarged. The brain and cord showed nothing unusual.

Diagnosis was asphyxia due to an aplasia of the right ventricle and the pulmonary arteries.

#### COMMENT

The probable circulation in this baby during life was from the right auricle to the vestige of the right ventricle into which a slight amount of blood went through a pinpoint opening of the tricuspid valve. From here the blood went into the small pulmonary artery to the lungs where this small amount was oxygenated; thence to the left auricle and through the systemic circulation in the usual manner.

It is possible also that the bronchial artery which normally supplies nutritive blood to the lungs, in this case carried some blood for oxygenation also, which then found its way through the pulmonary veins into the left auricle.

The amount of oxygenated blood was inadequate and we had cyanosis and later asphyxia of which the infant died, as indicated by the subepicardial hemorrhages found at postmortem.

Even had the foramen ovale been patent it would have made no difference in the amount of oxygenated blood in the system circulation in this case.

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**Lyons and VandeCour: Immunologic Aspects of the Sexual Cycle.** Arch. Path. 9: 1, 1931.

The authors in a series of tests with follicular fluids found that those of the sow, cow, mare, and ewe, are closely related immunologically. They found also that these same fluids are closely related to the follicular fluid of the guinea pig. The follicular fluid of the latter is also auto-antigenic. Guinea pigs artificially sensitized to follicular fluid proteins are temporarily desensitized by the liberation of their own follicular fluid. By the Dale-Schultz technic it was demonstrated that normal female guinea pigs become sensitized to their own follicular fluid at certain times during the estrus cycle. Fatal anaphylaxis may be produced at a definite time in normal guinea pigs, on primary injection of heterologous follicular fluid.

W. B. SERBIN.

**Vogt, E.: Temporary Hormonal Sterilization of Female Animals by Feeding Insulin.** Med. Klin. 15: 1163, 1929.

The author found that he could produce temporary hormonal sterilization in female animals by giving them insulin by mouth as well as by giving them insulin parenterally. This is proof that insulin is absorbed by the intestinal tract and is active after this mode of absorption. Since the female sex hormone in the form of folliculin, menformon and progynon, both experimentally in animals and clinically likewise is active when given orally and since the feeding of insulin to white mice produces temporary sterility without causing any general disturbances, Vogt believes this is further confirmation of his previously expressed belief that the pancreatic, the ovarian and the placental hormones are very closely related. Their action especially coincides in the production of sterility.

J. P. GREENHILL.

# American Journal of Obstetrics and Gynecology

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GEORGE W. KOSMAK, M.D., EDITOR

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## Editorial Comment

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### Pediatric Education

SECTION I on Medical Service of the White House Conference was made up of three committees. One dealt with problems of growth and development, another considered the questions involved in prenatal and maternal care, and a third was concerned with the medical care for children. The two last mentioned committees agreed in the conclusion that medical education was in reality the corner stone in any structure which might be erected to care for and improve the child life of the United States.

Some of the reports dealing with the educational problems in obstetrics presented to the committee on Prenatal and Maternal Care were published in the June number of this JOURNAL. At the final conference of the Section on Medical Service held in Washington, D. C., February, 1931, Borden S. Veeder, M.D., the chairman of the sub-committee on Medical Education, presented a noteworthy report dealing with pediatric education which has been published by the Century Company.

In the introduction to this report it is pointed out that the health problem is fundamental in all aspects of child life and that the science of medicine either is the basis upon which all health and welfare work stands or is intimately interwoven with all such projects. "The welfare nurse, the nutritional worker, the psychologist, and the medical social worker, are examples of specialized workers in the field of child health who are directly dependent upon the medical sciences for the basic knowledge of their work."

The fact is duly emphasized that the work with the delinquent, handicapped, school, home, or institutional child cannot be carried on efficiently and effectively without medical advice or supervision. The help and knowledge of the physician is essential for the adequate functioning of these various types of organizations. It must not be forgotten

that while various types of organized health work reach many children, "the vast majority of American children today are dependent upon the interest and care of a private physician for their physical well-being and health."

These considerations led this committee to undertake a study of the teaching of pediatrics and of current practice in the diseases of children.

The data and information which were gathered can be grouped under three main headings:

"A study of the practice of the physician in the field, and his opinion as to the adequacy or inadequacy of his medical school training in pediatrics.

"A study of the position pediatrics occupies in the medical school program, the hours allotted, subjects taught, etc., as well as facilities available.

"The demands and needs for postgraduate instruction and the opportunities available."

Most of this information was secured through the medium of questionnaires.

The number of hours suggested by the Committee amounts to about 8 per cent of the total number of hours allotted to the teaching of the clinical branches, or about two hundred hours. This is about one-fourth of the number allotted to each of the two major branches of medicine and surgery. A similar percentage is advised for obstetrics. It seems to me that the committee has been too modest and that preferably the ratio should have been: medicine is to surgery as obstetrics is to pediatrics, or approximately in the proportion of 2:2:1:1.\* The recommendations of the committee are very sane, and while brief, cover the essential points; for these reasons it seems worth while to quote them verbatim:

1. Pediatrics is a fundamental basic clinical subject and should be recognized as such by medical schools. The department of pediatrics should be independent and of equal academic rank with other departments, such as medicine.

2. Adequate teaching staff, hospital and clinic facilities, and laboratories should be provided and adequately financed.

3. The minimum teaching facilities should be:

Fifty beds for infants and children under the control of the head of the department.

Ten bassinets for newly born infants in a maternity hospital or division under the control of the pediatric department.

An out-patient clinic with a ratio of at least ten new pediatric admissions yearly for each student in the senior class.

A well-baby clinic for teaching normal feeding, growth, and development.

Affiliation with a hospital for "contagious" diseases.

Laboratories for routine and research work.

4. The course of undergraduate instruction should cover the following points: The physical and mental growth and development of the infant and child, and factors influencing them.

\*In this ratio medicine is meant to include all medical specialities other than pediatrics; surgery, all of the special surgical branches except gynecology which is included with obstetrics.

The nutritional requirements of infancy and childhood, including the feeding of normal infants and children.

The nutritional diseases of infancy and childhood and their treatment and prevention.

The "contagious" diseases: their recognition, prevention and treatment.

Diseases and pathologic conditions peculiar to early life.

The peculiar manifestations of certain diseases in infancy and childhood.

Environmental and hygienic factors which are important in early life.

Social aspects of pediatrics.

Certain special procedures.

The importance of specific preventive measures.

Certain conditions, the immediate recognition of which is essential to saving lives.

5. Two hundred hours should be the minimum time assigned to pediatrics in the four-year course. This will afford time for ward and clinic work in addition to standardized courses covering the subject. Electives in addition may be offered.

6. The teaching of pediatrics from a pedagogic standpoint should be carefully studied.

7. Intensive review courses (preferably of four weeks) should be continued for postgraduate students and attendance encouraged.

8. The extension courses at present given in some states should be continued, and started in states where they have not been introduced.

Accompanying this report are two leaflets with extracts from its discussion at the Conference. In one of them the author states, "I think as this report indicates, pediatrics should be related to medicine and surgery as one of the three important basic features, fundamental to the medical education of every student in the medical school," and again he adds, "Pediatrics, as I see it, is one of the three basic fundamental departments of medical instruction. It is more important, in many respects, than medicine or surgery. All study of human development must necessarily start at that important period of life, infancy." These statements are interesting, but perhaps should not be taken too seriously or literally inasmuch as they entirely eliminate obstetrics from the field of fundamental knowledge for the medical student. Any medical man knows that reproduction is fundamental and that obstetrics deals with this physiologic process in all its vagaries. Obstetrics\* is neither medicine nor surgery nor pediatrics, but surely requires at least a working knowledge of all these in addition to special knowledge in the individual field and should be listed as a special department. The study of growth and development begins, at the latest, with fertilization and not with infancy. Even the most ardent pediatrician should be willing to admit that if obstetrics were nothing more, it at least constitutes an important phase of preventive pediatrics.

The author of the other discussion states, "Since pediatrics deals with every phase of medicine except the disabilities incident to old age, much more space in the curriculum should be given to it than is now allotted to it by most schools." This seems to be a rather specious

\*In this discussion obstetrics also includes gynecology.

argument. One might assume that one legitimate theory of education would be that the instruction be given by those most expert in the respective specialties, and one might ask further if the stimulation of interest in a given field and the creation of a desire to know is not more important than the number of hours in the curriculum. It is quite possible that the student might acquire more in a few hours from some teachers, in the way of real stimulation of interest than from others in two hundred hours recommended for pediatrics or any other branch.

It might be seriously questioned as to whether or not the student is burdened with too many required hours of instruction. Too much instruction leaves little time for individual effort and not enough opportunity for thinking. Again, it is not necessarily a foregone conclusion that the subject matter taught should always fall in the same department in different schools. The one on the faculty who knows most about a given subject should teach it irrespective of the department with which he is connected.

There was a definite recognition given by the White House Conference to the importance of obstetrics in relation to child health and protection. It would be exceedingly unfortunate if the remarks made in the discussion of Veeder's report should be taken too literally and too authoritatively. Obstetrics is fundamental and most pediatricians should be willing to admit that the relationship between these two branches of medicine is almost as close as that between mother and child. In education in general, and especially in medical education, the important factors are facilities, and the best type of teachers and students.

*Fred L. Adair, M.D.*

## Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D., ASSOCIATE EDITOR

### Selected Abstracts

#### Endocrinology

**Scibelli: Research on the Utero-ovarian Modifications in Experimental Hyperthyroidism.** Arch. Ostet. e Ginec. 16: 1008, 1929.

In normal rabbits, the thyroid hormone, experimentally used, accentuates the phenomena, first of growth and then of regression of the uterine mucosa; and at the same time one notes strong evidence of maturation of ovarian follicles, and notable hypertrophy of corpora lutea. In castrated rabbits, the findings are disorderly possibly due to alterations brought about by castration. This leads the author to think that thyroid and a specific hormone of the ovary regulate between themselves the rhythmic uterine cycle.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Arbuzese: Thyroid Function in the So-called Essential Metrorrhagias.** Riv. Ital. di Ginec. 8: 5, 1929.

Nearly all investigators admit the existence of an ovarian-thyroid antagonism, expressed in hyperthyroidism during pregnancy, in climaacterium and following castration, that is, ovarian hypofunction leads to thyroid hyperfunction. The ovary has hypotensive and the thyroid hypertensive activity. The ovary may cause bradycardia, the thyroid a tachycardia. The antagonism manifests itself chiefly in the sexual functions. Admitting such antagonism, in cases of metrorrhagias a primary hyperovarism might be succeeded by hypothyroidism.

In the last analysis there are at least two types of pubertal metrorrhagias, one connected with primary hyperovarism followed by thyroid hypofunction, and another with constitutional hypothyroidism preceding sexual development.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Gilardino: Folliculine and Thyroid.** Riv. Ital. di Ginec. 11: 3, 1930.

Folliculine, administered subcutaneously to animals is very well tolerated and causes no disturbances even when administered for a long time.

Besides the well known modifications of the genital organs it has the property of bringing about distinct hyperemia of the parenchymatous organs and hypertrophy of the thyroid.

The thyroid hypertrophy observed in pregnancy must be attributed to the greater quantity of follicular hormone.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Paroli: Research Studies and Clinical Results on Diathermy of the Thyroid on the Essential Metrorrhagias.** Arch. di Biol. Norm. e Patol. 84: 1, 1930.

In the metrorrhagias of puberty one often observes a functional deficiency of the thyroid. After the diathermic treatment of the thyroid greater activity of this gland is noticed while at the same time the metrorrhagias improve and eventually cease. Such improvement lasts only three or four months.

In all cases of metrorrhagia near the climacterium sterilizing Roentgen or radium therapy is preferable.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Abruzzese: The Functional Status of the Thyroid in the Pathogenesis of Abortion.**

Riv. Ital di Ginec. 10: 1, 1929.

An endocrine abnormal function of the thyroid constitutes, probably very often, the pathogenic substratum of certain abortions whose pathology is obscure. Both hypo- and hyper-thyroidism seem to disturb the evolution of pregnancy, hyperthyroidism especially in early pregnancy and in the pluripara. This might be interpreted as a precocious and exaggerated awakening of the pregnant hyperactivity of the thyroid at the second half of pregnancy.

A functional examination of the thyroid made promptly inryptogenie abortions is indicated, since it might lead to an opportune therapeutic finding, both for prevention and cure.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Fahrni, Gordon S.: Pregnancy Complicating Hyperthyroidism and Following Thyroidectomy.** Canadian M. A. J. 23: 645, 1930.

The author recommends thyroidectomy for those less than five months pregnant as there is little increased risk. After the fifth month operation should be deferred until after delivery. Pregnancies should be avoided for two years. Therapeutic terminations have no place because they are associated with greater danger than the other forms of treatment.

H. C. HESSELTINE.

**Hartley, E. C.: The Tetanoid Syndrome in Pregnancy.** Minn. Med. 13: 190, 1930.

Another case illustrating the tetanoid syndrome in pregnancy is reported by the author. The patient was a para x, 36 years old, and presented edema of the extremities, insomnia, irritability, crampy pains, and paresthesias that make up the syndrome. Administration of parathormone and calcium produced striking and immediate relief. The condition is probably due to a relative hypocalcemia.

FRANK SPIELMAN.

**Stevens, Neil Campbell: The Thyroid and Headache at the Menopause.** New Engl. J. Med. 201: 168, 1929.

It appears that there is a definite complex occurring in women between the ages of forty-five and sixty, which is characterized by headache, fatigue, nervousness, subnormal temperature, dry skin, sensitiveness to cold and a low or subnormal basal metabolic rate. Such patients are benefited by the administration of thyroid extract.

EHRENFEST.

**Schultze-Rhonof and Niedenthal: Researches Concerning the Hormonal Value of the Anterior Lobe of the Fetal Hypophysis in Animal Experiments.** Zentralbl. f. Gynäk. 53: 902, 1929.

In an attempt to prove the presence of the anterior pituitary hormone in the pituitary body of human and cattle fetuses, the authors implanted anterior lobes of 25 human and several cattle fetuses in infantile mice. The typical reactions of opening of the vagina, enlargement of both horns of the uterus, and follicle formation in the ovaries, were observed in all cases. They, therefore, believe to have proved the presence of the anterior pituitary hormone in the fetus.

WILLIAM F. MENGERT.

**Philipp, E.: Anterior Pituitary and Placenta.** Zentralbl. f. Gynäk. 54: 450, 1930.

The author believes that the pregnancy reaction of Aschheim-Zondek is in reality a placental reaction. To support this view he submits the following evidence: The chorionic villi of a human tubal pregnancy of two or three months were implanted into infantile mice and without a single exception all showed an enormous change in the ovaries similar to the changes obtained in the AZ reaction. Amniotic fluid, the amnion itself from an early pregnancy, and decidua everted from a case of tubal pregnancy, gave a similar, but not so strong, reaction. Similar injections and implantations into castrated mice gave no reaction of estrus. Placental implantations of early abortions gave positive tests in cases which had showed a positive AZ reaction, and negative tests in cases which had showed a negative AZ reaction. Implantation of placentae from patients at term gave a very weak reaction discernible only on microscopic serial sections. Direct implantation into mice of anterior pituitary lobes taken directly from 4 patients, 3 of whom died postpartum after term pregnancies, and one who died after abortion in the third month, gave no ovarian change. However, implantation of 3 anterior pituitary lobes taken from nonpregnant women did give typical changes, i.e., follicular bleeding and corpora lutea atretica. The author hesitates to draw too many conclusions from a research which is just beginning, but he does state quite positively that the Aschheim-Zondek reaction results from products of pregnancy and not from the anterior lobe of the pituitary gland.

WILLIAM F. MENGERT.

**Scaglione: Fibroma of the Uterus and Hypophysis.** Arch. Ital. di Ginec. 11: 2, 1930.

It is noteworthy that fibromas develop: (1) Only exceptionally before puberty and after the menopause. It is therefore a tumor that coincides with the greatest activity of the ovary. (2) After menopause many fibromas undergo retrograde changes. (3) Histologic analogies exist between uterine hyperplasia in pregnancy and localized hyperplasia of the foci of myomas. (4) The fibroma is rare in the neck of the uterus, a region not participating in ovarian growth activity. (5) The fibroma is frequent in sterile females.

Existing relations between ovary and hypophysis can be thus demonstrated: (1) The total ablation of the anterior lobe of the hypophysis in immature animals leads to a cessation of development of ovary and uterus. (2) Total ablation of the anterior lobe of the hypophysis in mature animals leads to a rapid diminution of the weight of the ovary with stoppage of the maturation of graafian follicles and of ovulation, with disappearance of the corpora lutea. At the same time the uterus undergoes atrophic changes with cessation of its cyclic activity. (3) The homo- and the hetero-transplant of hypophyseal tissue in animals deprived of hypophysis leads to an increase in weight of the ovary, a return of functional activity and an

increase in the volume of the uterus. (4) Transplants of hypophyseal fragments to immature animals lead to a rapid increase in weight of the ovary, an increase in the Graafian follicles and to a considerable hypertrophy of the uterus.

These and other factors would justify the conclusion that the hypophysis exercises a direct effect on a fibroma, possibly since it modifies ovarian activity.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Candela: Follicular, Luteinic and Mammarian Incretotherapy and Its Influence on the Genital Tract and on the Endocrine System. Experimental Study.** Arch. Ostet. e Ginec. 17: 97, 1930.

The author from studies on guinea pigs treated with follicular, luteinic and mammarian extracts, arrives at the following results:

The follicular extract is responsible for a more accentuated development of the genital tract, the maturation of the ovarian follicles and the prolongation and intensification of the estrus cycle; the other extracts may determine alterations in the rhythm of the estrus cycle or else in its suppression; the mammarian extract may lead to atrophy of the ovary and of the genital tract. The thyroid and the mammary gland are slightly hypertrophied with the follicular extracts, this condition is more marked with luteinic and mammarian extracts.

Notable hypertrophy is also obtained in the suprarenals and in the hypophysis by the action of the follicular and mammarian extracts. With the luteinic extracts, on the other hand, there is obtained atrophy of the hypophysis and moderate hypertrophy of the suprarenals.

Finally, the luteinic and mammarian extracts lead to an increase in weight of the animal, but confer sterility; the follicular extract has no influence on the body weight and augments fecundability.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Bisceglie: The Effects of Hyperhormonization With Follicular Liquids on Hypophysis, Thyroid and Suprarenals.** Endocrinol. e Patol. Costit. 5: 70, 1930.

The results obtained with the administration of follicular liquid are: (1) Hypophysis (anterior lobe) modifications are seen which augment in intensity parallel to the follicular liquid administration. These modifications consist in hyperemia with a constant increase of the acidophilic, disappearance of the basophilic cells and some increase of colloid. (2) There is a gradual reduction of the volume of the thyroid cells, showing a smaller quantity of colloid, and a notable hyperplasia of the intercellular epithelium.

(3) With short treatment no defined changes are seen in the suprarenal cortex. With longer administration of the liquid, there is a slight hyperemia, changes in the spongy tissue in the zona reticulata and fasciculata, with considerable increase in these zones of lipid substances. In the medullar region no appreciable changes are observed.

SYDNEY S. SCHOCHET.  
JULIUS E. LACKNER.

**Siegmund: The Dependence of the Uterine Musculature Upon the Function of the Ovary.** Arch. f. Gynäk. 140: 573 and 583, 1930.

The author based his studies on the investigations of Knaus who found by experiments on rabbits that the corpus luteum hormone inhibits the effect of the pituitary hormone upon the uterine musculature. Siegmund finds that this relation-

ship does not hold for the rat. There probably is a difference in the corpus luteum of the rabbit and that of the rat. The corpus luteum is indispensable in the rat as well as in the rabbit, for its removal always causes fetal death. The difference in sensitivity to pituitary hormone as demonstrated to exist in rabbit and rat is new evidence of varying and often opposite reactions of the same organs in different species to the hormones of similar organs.

RALPH A. REIS.

**Knaus, H.: Physiology of the Corpus Luteum.** Arch. f. Gynäk. 141: 374, 1930.

The author has conducted a large series of experiments and studies of the reproductive functions of the rabbit with special reference to the corpus luteum. He concludes: False pregnancy in the rabbit lasts sixteen days. The corpus luteum thirty-two hours postcoitum produces changes in the uterus which prevent the latter from reacting to the posterior pituitary extract. The corpus luteum stimulates a marked hypertrophy and hyperplasia of the endometrium and the mammary glands. It also inhibits the follicle ripening and ovulation. Removal of the corpus luteum stops all these reactions. It requires about ten hours for the uterus to react to pituitary extract following extirpation of the corpus luteum. In pregnancy, in the rabbit, the corpus luteum activity begins to decrease on the eighteenth day but some function persists until just before delivery, which usually occurs on the thirty-second day. The stimulation of the uterus and the mammary glands by the corpus luteum of pregnancy is more marked than in false pregnancy. This difference in reaction is demonstrable on the tenth day postcoitum, and thus the true corpus luteum can be differentiated from the false. The latter becomes a true corpus luteum of pregnancy only through the stimulation of the hormone of the ovum. The corpus luteum prevents the entire pituitary gland from exciting any influence on the female genitalia. The cyclic character of the ovarian function is dependent upon the corpus luteum.

RALPH A. REIS.

**Brande and Schwarzmann: The Effect of Iodine on the Ovary.** Arch. f. Gynäk. 138: 782, 1929.

The authors studied the effects of continued and repeated administration of iodine on female experimental animals. In each instance one ovary was first removed and studied as the control. The iodine was then given by hypodermic over varying periods of time and in varying dosages. The second ovary was then removed and examined grossly as well as microscopically. They found that in mature animals, iodine produces destructive changes in the ovary manifested by degeneration and destruction of the follicular apparatus. The extent of this destruction depends not so much upon the amount of iodine administered as upon the length of time during which it is given. The cyclic changes in the vaginal mucosa of mice are lost and the iodinized animals are sterile. None of these results could be obtained by the injection of foreign protein.

RALPH A. REIS.

**Bruehl: The Occurrence of the Female Sex Hormone in the Blood and Urine of the Newborn.** Klin. Wehnschr. 8: 1766, 1929.

The female sex hormone is found in the blood and the urine of the newborn irrespective of sex. It is found for the first four days of extrauterine life and is also constantly present in the amniotic fluid and in the umbilical cord blood. On the other hand, the hormone of the anterior lobe of the pituitary is found in the urine of the newborn for only the first two days and then in only approximately

50 per cent of the babies. This pituitary hormone is always demonstrable in umbilical cord blood but only in very small amounts. In milk its presence was only demonstrated in one instance and it was never found in the amniotic fluid.

Animal experiments show definitely that the female sex hormone disappears from the body as the glands of the breasts become active. The female sex hormone most probably disappears from the newborn for the same reason, viz., the activation of the secretory glands of the breasts.

RALPH A. REIS.

**Siebert: The Results of Ovarian Transplantation After Loss of Both Ovaries.**

Med. Klin. 25: 1845 and 1884, 1929.

Nine women between the ages of twenty-three and thirty-seven had their ovaries removed chiefly because of inflammatory conditions, but their uteri were left. In all of them autoplastic transplantation of the ovaries was performed and the site of implantation was the anterior rectus fascia. These patients were closely followed by Siebert and he came to the conclusion that in most cases of ovarian transplantation there is a more or less rapid disintegration of the ovarian tissue. In the cases studied there was neither a return of the regular menses nor an amelioration of menopausal symptoms.

J. P. GREENHILL.

**Aschner, E.: Menstrual Disorders as Causes of Disease. II. Joint Diseases Resulting From Too Infrequent or Scanty Menstruation.** Wien. klin. Wehnschr. 42: 322, 1929.

As stated in a previous paper, menstruation in normal quantity at regular intervals of 4 weeks is a necessity for the healthy woman. Whether it is associated with ovarian secretion, as most authors believe, or whether the flow represents an excretion following metabolic changes, as Aschner believes, is of secondary importance. However, it has been shown repeatedly that too infrequent or scanty menstruation in younger women as well as the production of an early artificial climacterium has been accompanied by obesity, plethora, susceptibility to infections and metabolic changes, dyscrasias in the truest sense of the word.

Of 700 hypomenorrhoeic patients, 230 (about one-third) showed arthritic-rheumatic-neuralgic conditions, 74 of whom had joint pains whose severity depended definitely on the quantity of blood lost at menstruation.

The ovary plays a part in the process, which is complicated and little understood; certainly ovarian therapy is not nearly as efficacious as the author's treatment consisting in emmenagogues, and antidyseas, especially antiarthritic measures.

All the arthropathies, which the author divides into 4 groups, (a) painful joints with and without swelling or deformity, (b) a combination of joint pains with rheumatic pains in muscles, ligaments, and tendon sheaths, (c) joint affections plus neuralgic conditions, (d) a combination of the above three, are accompanied with surprising frequency by hypomenorrhea. Careful questioning of the patients also elicits the information that these pains are worse before, and better after menstruation. The relationship is best brought out, however, by the frequency of joint affections when menopause is produced artificially. Accompanying metabolic disturbances tend to favor a kind of auto-intoxication, and are prone to improve when the "blood clearing" measures are instituted.

Aschner's treatment consists in: (1) The use of strong emmenagogues—tincture of aloes, up to 30 min. three times a day; infusion of senna, and Ruffi's pill (a mixture of aloes, myrrh, and crocus) are especially recommended. (2) Measures help-

ing elimination through intestines and kidneys. (3) The strongest measures promoting elimination through the skin—the cantharides plaster is here mentioned as particularly efficacious.

In concluding the author proposes "arthropathia hypomenorrhoea" as a term characterizing the above conditions.

FRANK SPIELMAN.

**Lauber and Ramm: Prognosis and Therapy of Arthropathia Ovaripriva.** München. med. Wehnschr. 77: 89, 1930.

The authors describe a type of joint affection, which develops during the menopause and is directly attributable to lack of ovarian hormone. They comment on reports of joint lesions, attributed to hyperthyroidism and other endocrine disturbances. Arthropathia ovaripriva is characterized at first, by tingling and pain, particularly in the small phalangeal, and later in the carpo-metacarpal joints, and finally in the knee-joints. These symptoms are particularly noticed when the patient moves from cold outdoor temperatures into a warm room. They are probably due to vascular spasm. Objectively, the joints are found thickened and slightly swollen. Motion, active and passive, is limited and painful. There are no signs of acute inflammation. X-ray shows very little in early cases; in late cases, changes similar to those of arthritis deformans are seen.

The important feature of the treatment is the administration of an active ovarian hormone. In 6 early cases, the authors obtained cures by giving such a preparation by mouth (Ovoglandol or Menformon-Laquer), in addition to potassium iodid and alternate hot and cold baths. Improvement was evident in three to six weeks, and complete cure in six to twelve weeks. Three late cases were improved, but not cured, by these measures plus baking, massage, diathermy, etc.

A. SHULMAN.

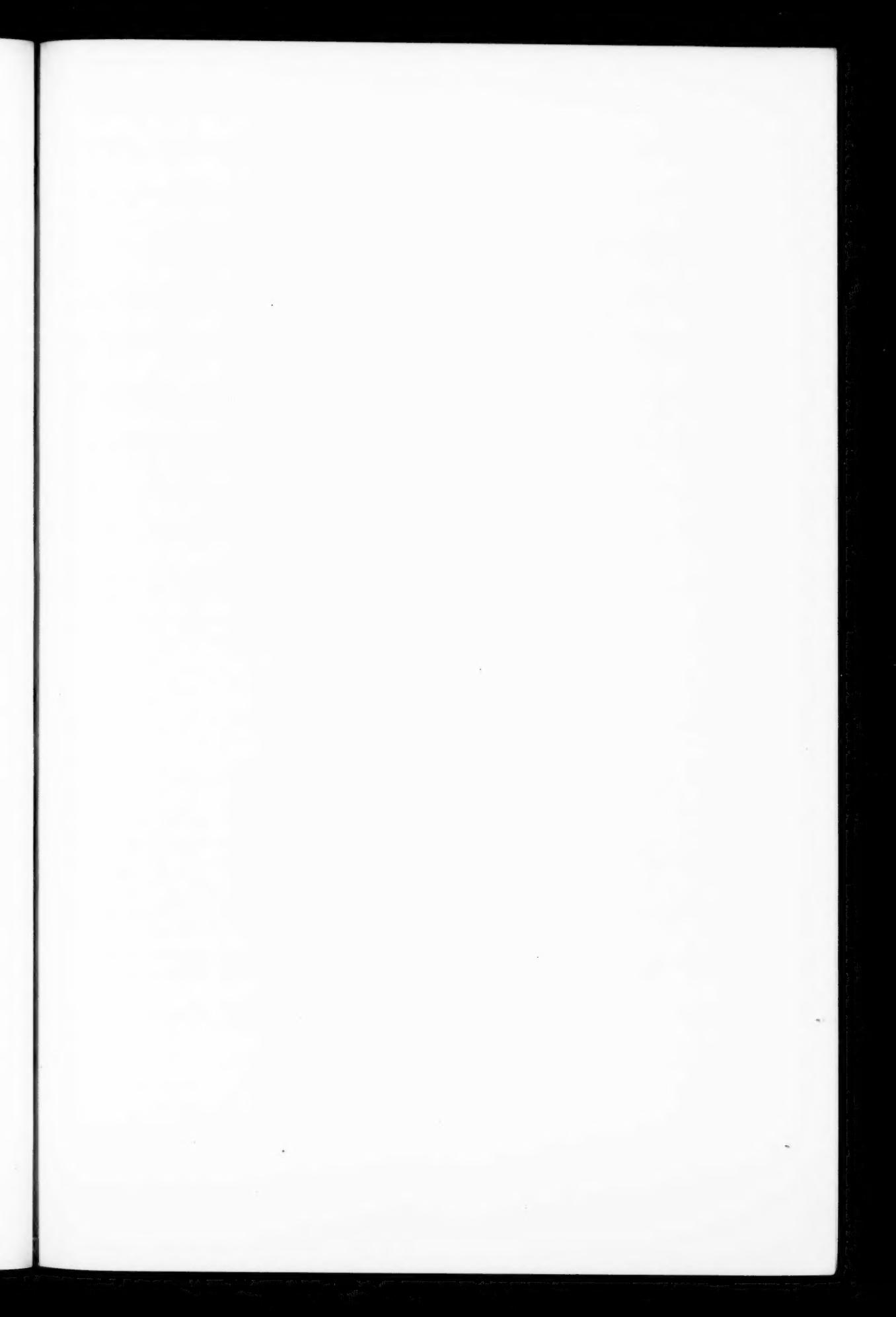
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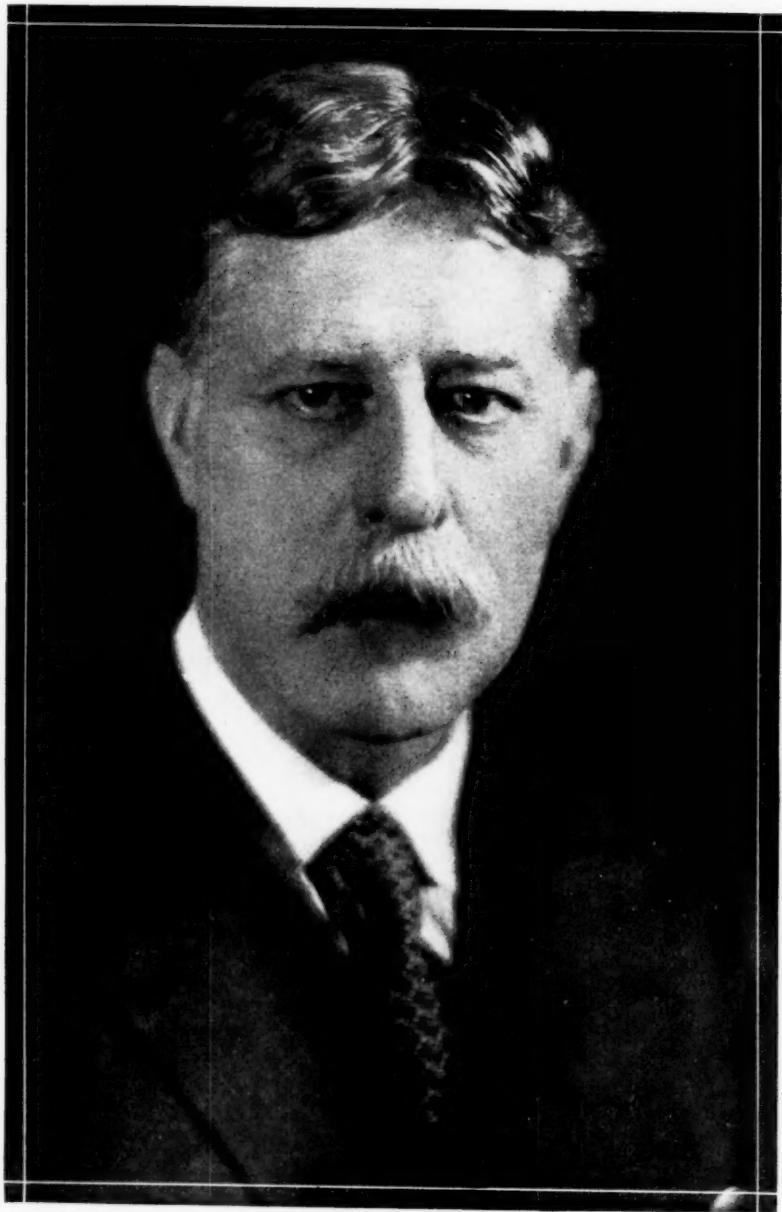
#### ITEM

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#### **American Board of Obstetrics and Gynecology**

The next written examination for Group III candidates for certificate from this Board will be held in 18 cities of this country and Canada on Saturday, October 31, at 2 P.M. The clinical examination for all candidates will be held at the Chicago Lying-In Hospital, Chicago, Ill., on Tuesday, December 29, at 9 A.M. For further information address the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pa.





JOHN WHITRIDGE WILLIAMS  
1866-1931